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PCT/EP2004/052262
21.09.04

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten internationalen Patentanmeldung überein.

The attached documents are exact copies of the international patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet international spécifiée à la page suivante.

Den Haag, den
The Hague,
La Haye, le

10. 12. 2004

Der Präsident des Europäischen Patentamts
Im Auftrag
For the President of the European Patent Office
Le Président de l'Office européen des brevets
p.o.

R. de Bes

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Patentanmeldung Nr.
Patent application no.
Demande de brevet n° PCT/EP 03/50659

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Demande n°: PCT/EP 03/50659

Anmelder:
Applicant(s):
Demandeur(s):
1. JANSSEN PHARMACEUTICA N.V - Beerse, Belgium
2. JANSSEN, Paul, Adriaan, Jan - Beerse, Belgium (US only)
3. LEWI, Paulus, Joannes - Beerse, Belgium (US only)

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Further applicants:

4. DE JONGE, Marc, René - Beerse, Belgium (US only)
5. KOYMANS, Lucien, Maria, Henricus - Beerse, Belgium (US only)
6. DAEYAERT, Frederik, Frans, Desiré - Beerse, Belgium (US only)
7. HEERES, Jan - Beerse, Belgium (US only)
8. VINKERS, Hendrik, Maarten - Beerse, Belgium (US only)
9. LEENDERS, Ruben, Gerardus, George - Nijmegen, The Netherlands (US only)
10. VANDENPUT, Dirk, Alfons, Leo - Nijmegen, The Netherlands (US only)

PCT REQUEST

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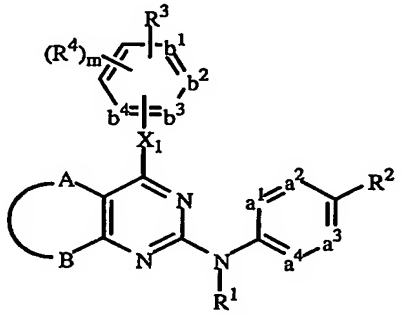
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
IV-1-1	Name	JANSSEN PHARMACEUTICA N.V.
IV-1-2	Address:	Turnhoutseweg 30 B-2340 Beerse Belgium
IV-1-3	Telephone No.	00 32 14 60 38 34
IV-1-4	Facsimile No.	00 32 14 60 54 91
IV-1-5	e-mail	patents@janbe.jnj.com
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	US
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI	**Priority claim**	NONE
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)

HIV REPLICATION INHIBITING PURINE DERIVATIVES

The present invention is concerned with purine derivatives having HIV (Human Immunodeficiency Virus) replication inhibiting properties. The invention further relates to methods for their preparation and pharmaceutical compositions comprising them. The invention also relates to the use of said compounds for the manufacture of a medicament for the prevention or the treatment of HIV infection.

The compounds of the invention differ from the prior art compounds in structure, pharmacological activity and/or pharmacological potency.
Unexpectedly, it has been found that the compounds of the invention have an improved ability to inhibit the replication of Human Immunodeficiency Virus (HIV), in particular they have an improved ability to inhibit the replication of mutant strains, i.e. strains which have become resistant to art-known drug(s) (drug or multidrug resistant HIV strains).

The present invention concerns a compound of formula



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

$-a^1=a^2-C(R^2)=a^3-a^4=$ represents a bivalent radical of formula

$-CH=CH-C(R^2)=CH-CH=$ (a-1);

$-N=CH-C(R^2)=CH-CH=$ (a-2);

$-CH=N-C(R^2)=CH-CH=$ (a-3);

$-N=CH-C(R^2)=N-CH=$ (a-4);

$-N=CH-C(R^2)=CH-N=$ (a-5);

$-CH=N-C(R^2)=N-CH=$ (a-6); or

$-N=N-C(R^2)=CH-CH=$ (a-7);

$-b^1=b^2-b^3=b^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (b-1);
-N=CH-CH=CH- (b-2);
-N=CH-N=CH- (b-3);
-N=CH-CH=N- (b-4); or
-N=N-CH=CH- (b-5);

-A-B- represents a bivalent radical of formula
-N=CH-NR^{17}- (c-1); or
-NR^{17}-CH=N- (c-2);

m is 1, 2, 3 and in case -b^1=b^2-b^3=b^4- is (b-1), then m may also be 4;

R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^2 is cyano; aminocarbonyl; mono- or di(C_{1-4}alkyl)aminocarbonyl; C_{1-6}alkyl; C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl; C_{2-6}alkenyl; C_{2-6}alkenyl substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl; C_{2-6}alkynyl; or C_{2-6}alkynyl substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl;

X_1 is –NR^5-, -NH-NH-, -N=N-, -O-, -C(=O)-, C_{1-4}alkanediyl, -CHOH-, -S-, -$S(=O)_p$-, -X_2-C_{1-4}alkanediyl- or –C_{1-4}alkanediyl-X_2-;

X_2 is –NR^5-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -$S(=O)_p$-;

R^3 is NHR^{13}; $NR^{13}R^{14}$; -C(=O)-NHR^{13}; -C(=O)-$NR^{13}R^{14}$; -C(=O)-R^{15}; -CH=N-NH-C(=O)-R^{16}; cyano; halo; C_{1-6}alkyl; polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or more substituents each independently selected from cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; C_{1-6}alkyl substituted with hydroxy and a second substituent selected from cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; C_{1-6}alkyloxyC_{1-6}alkyl optionally substituted with one or more substituents each independently selected from cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; C_{1-6}alkyloxy optionally substituted with one or more substituents each independently selected from cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; C_{2-6}alkenyl optionally substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; C_{2-6}alkynyl optionally substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; -C(=N-O-R^8)-C_{1-4}alkyl; R^7 or –X_3-R^7;

X_3 is $-NR^5-$, -NH-NH-, -N=N-, -O-, -C(=O)-, -S-, $-S(=O)_p-$, $-X_{2b}-C_{1-4}$alkanediyl-, $-C_{1-4}$alkanediyl-$X_{2a}-$, $-C_{1-4}$alkanediyl-$X_{2b}-C_{1-4}$alkanediyl, $-C(=N-OR^8)-C_{1-4}$alkanediyl-;

with X_{2a} being -NH-NH-, -N=N-, -O-, -C(=O)-, -S-, $-S(=O)_p-$; and

with X_{2b} being -NH-NH-, -N=N-, -C(=O)-, -S-, $-S(=O)_p-$;

each R^4 independently is halo, hydroxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyl, formyl, amino, mono- or di(C_{1-4}alkyl)amino or R^7;

R^5 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl or C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^6 is C_{1-4}alkyl, amino, mono- or di(C_{1-4}alkyl)amino or polyhaloC_{1-4}alkyl;

R^7 is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems may optionally be substituted where possible with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, formyl, C_{1-6}alkylcarbonyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthio, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, $-CH(=N-O-R^8)$, R^{7a}, $-X_3-R^{7a}$ or $R^{7a}-C_{1-4}$alkyl;

R^{7a} is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems may optionally be substituted where possible with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, formyl, C_{1-6}alkylcarbonyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthio, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, $-CH(=N-O-R^8)$;

R^8 is hydrogen, C_{1-4}alkyl, aryl or arylC_{1-4}alkyl;

R^9 and R^{10} each independently are hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; amino; mono- or di(C_{1-6}alkyl)amino; mono- or

di(C_{1-6}alkyl)aminocarbonyl; -CH(=NR^{11}) or R^7, wherein each of the aforementioned C_{1-6}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-4}alkyl)amino, polyhaloC1-4alkyl, polyhaloC1-4alkyloxy, polyhaloC1-4alkylthio, -S(=O)$_p$$R^6$, -NH-S(=O)$_p$$R^6$, -C(=O)$R^6$, -NHC(=O)H, -C(=O)$NHNH_2$, -NHC(=O)$R^6$,-C(=NH)$R^6$, R^7; or

R^9 and R^{10} may be taken together to form a bivalent or trivalent radical of formula

$-CH_2-CH_2-CH_2-CH_2-$	(d-1);
$-CH_2-CH_2-CH_2-CH_2-CH_2-$	(d-2);
$-CH_2-CH_2-O-CH_2-CH_2-$	(d-3);
$-CH_2-CH_2-S-CH_2-CH_2-$	(d-4);
$-CH_2-CH_2-NR^{12}-CH_2-CH_2-$	(d-5);
$-CH_2-CH=CH-CH_2-$	(d-6); or
=CH-CH=CH-CH=CH-	(d-7);

R^{11} is cyano; C_{1-4}alkyl optionally substituted with C_{1-4}alkyloxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino or aminocarbonyl; C_{1-4}alkylcarbonyl; C_{1-4}alkyloxycarbonyl; aminocarbonyl; mono- or di(C_{1-4}alkyl)aminocarbonyl;

R^{12} is hydrogen or C_{1-4}alkyl;

R^{13} and R^{14} each independently are C_{1-6}alkyl optionally substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl;

C_{2-6}alkenyl optionally substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl;

C_{2-6}alkynyl optionally substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl;

R^{15} is C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl;

R^{16} is C_{1-6}alkyl optionally substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl; or R^7;

R^{17} is hydrogen;C_{1-6}alkyl; or C_{1-6}alkyl substituted with aryl;

p is 1 or 2;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthio, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, R^7 or -X_3-R^7.

As used hereinbefore or hereinafter C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl; C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the group defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylbutyl and the like; C_{1-4}alkanediyl defines straight or branched chain saturated bivalent hydrocarbon radicals having from 1 to 4 carbon atoms such as methylene, 1,2-ethanediyl or 1,2-ethylidene, 1,3-propanediyl or 1,3-propylidene, 1,4-butanediyl or 1,4-butylidene and the like; C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{2-6}alkenyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a double bond such as ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like; C_{2-6}alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a triple bond such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like; a monocyclic, bicyclic or tricyclic saturated carbocycle represents a ring system consisting of 1, 2 or 3 rings, said ring system being composed of only carbon atoms and said ring system containing only single bonds; a monocyclic, bicyclic or tricyclic partially saturated carbocycle represents a ring system consisting of 1, 2 or 3 rings, said ring system being composed of only carbon atoms and comprising at least one double bond provided that the ring system is not an aromatic ring system; a monocyclic, bicyclic or tricyclic aromatic carbocycle represents an aromatic ring system consisting of 1, 2 or 3 rings, said ring system being composed of only carbon atoms; the term aromatic is well known to a person skilled in the art and designates cyclically conjugated systems of $4n + 2$ electrons, that is with 6, 10, 14 etc. π-electrons (rule of Hückel) ; a monocyclic, bicyclic or tricyclic saturated heterocycle represents a ring system consisting of 1, 2 or 3 rings and comprising at least one heteroatom selected from O, N or S, said ring system containing only single bonds; a monocyclic, bicyclic or tricyclic partially saturated heterocycle represents a ring system consisting of 1, 2 or 3 rings and comprising at least one heteroatom selected from O, N or S, and at least one double bond provided that the ring system is not an aromatic ring system; a monocyclic, bicyclic or tricyclic aromatic heterocycle represents an aromatic ring system consisting of 1, 2 or 3 rings and comprising at least one heteroatom selected from O, N or S.

Particular examples of monocyclic, bicyclic or tricyclic saturated carbocycles are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[4,2,0]octanyl, cyclononanyl, cyclodecanyl, decahydronapthalenyl, tetradecahydroanthracenyl and the like.

Particular examples of monocyclic, bicyclic or tricyclic partially saturated carbocycles are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, bicyclo[4,2,0]octenyl, cyclononenyl, cyclodecenyl, octahydronaphthalenyl, 1,2,3,4-tetrahydronaphthalenyl, 1,2,3,4,4a,9,9a,10-octahydro-anthracenyl and the like.

Particular examples of monocyclic, bicyclic or tricyclic aromatic carbocycles are phenyl, naphthalenyl, anthracenyl.

Particular examples of monocyclic, bicyclic or tricyclic saturated heterocycles are tetrahydrofuranyl, pyrrolidinyl, dioxolanyl, imidazolidinyl, thiazolidinyl, tetrahydrothienyl, dihydrooxazolyl, isothiazolidinyl, isoxazolidinyl, oxadiazolidinyl, triazolidinyl, thiadiazolidinyl, pyrazolidinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyrazinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, trithianyl, decahydroquinolinyl, octahydroindolyl and the like.

Particular examples of monocyclic, bicyclic or tricyclic partially saturated heterocycles are pyrrolinyl, imidazolinyl, pyrazolinyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, indolinyl and the like.

Particular examples of monocyclic, bicyclic or tricyclic aromatic heterocycles are azetyl, oxetylidenyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, pyranyl, benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolizinyl, indolyl, isoindolyl, benzoxazolyl, benzimidazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, benzopyrazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinolizinyl, phthalazinyl, quinoxalinyl, quinazolinyl, naphthiridinyl, pteridinyl, benzopyranyl, pyrrolopyridyl, thienopyridyl, furopyridyl, isothiazolopyridyl, thiazolopyridyl, isoxazolopyridyl, oxazolopyridyl, pyrazolopyridyl, imidazopyridyl, pyrrolopyrazinyl, thienopyrazinyl, furopyrazinyl, isothiazolopyrazinyl, thiazolopyrazinyl, isoxazolopyrazinyl, oxazolopyrazinyl, pyrazolopyrazinyl, imidazopyrazinyl, pyrrolopyrimidinyl, thienopyrimidinyl, furopyrimidinyl, isothiazolopyrimidinyl, thiazolopyrimidinyl, isoxazolopyrimidinyl, oxazolopyrimidinyl, pyrazolopyrimidinyl, imidazopyrimidinyl, pyrrolopyridazinyl, thienopyridazinyl, furopyridazinyl, isothiazolopyridazinyl, thiazolopyridazinyl, isoxazolopyridazinyl, oxazolopyridazinyl, pyrazolopyridazinyl, imidazopyridazinyl, oxadiazolopyridyl,

thiadiazolopyridyl, triazolopyridyl, oxadiazolopyrazinyl, thiadiazolopyrazinyl, triazolopyrazinyl, oxadiazolopyrimidinyl, thiadiazolopyrimidinyl, triazolopyrimidinyl, oxadiazolopyridazinyl, thiadiazolopyridazinyl, triazolopyridazinyl, imidazooxazolyl, imidazothiazolyl, imidazoimidazolyl, isoxazolotriazinyl, isothiazolotriazinyl, pyrazolotriazinyl, oxazolotriazinyl, thiazolotriazinyl, imidazotriazinyl, oxadiazolotriazinyl, thiadiazolotriazinyl, triazolotriazinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhalomethyl as a group or part of a group is defined as mono- or polyhalosubstituted methyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl; polyhaloC_{1-4}alkyl or polyhaloC_{1-6}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-4}alkyl or C_{1-6}alkyl, for example, the groups defined in halomethyl, 1,1-difluoro-ethyl and the like. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhalomethyl, polyhaloC_{1-4}alkyl or polyhaloC_{1-6}alkyl, they may be the same or different.

The term heterocycle in the definition of R^7 or R^{7a} is meant to include all the possible isomeric forms of the heterocycles, for instance, pyrrolyl comprises 1*H*-pyrrolyl and 2*H*-pyrrolyl.

The carbocycle or heterocycle in the definition of R^7 or R^{7a} may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate, if not otherwise specified. Thus, for example, when the heterocycle is imidazolyl, it may be 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and the like, or when the carbocycle is naphthalenyl, it may be 1-naphthalenyl, 2-naphthalenyl and the like.

When any variable (eg. R^7, X_2) occurs more than one time in any constituent, each definition is independent.

Lines drawn from substituents into ring systems indicate that the bond may be attached to any of the suitable ring atoms.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxy-acetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline, the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyliodide or benzyliodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several tertiary nitrogen atoms are oxidized to the so-called *N*-oxide.

It will be appreciated that some of the compounds of formula (I) and their *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I), and their *N*-oxides, addition salts, quaternary amines or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) and their *N*-oxides, salts, solvates or quaternary amines substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. Thus, when a compound of formula (I) is for instance specified as (E), this means that the compound is substantially free of the (Z) isomer.
In particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-configuration. Compounds encompassing double bonds can have an E (entgegen) or Z (zusammen) -stereochemistry at said double bond. The terms cis, trans, R, S, E and Z are well known to a person skilled in the art.
Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

For some of the compounds of formula (I), their prodrugs, *N*-oxides, salts, solvates, quaternary amines or metal complexes and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined. In these cases the stereoisomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" stereoisomeric forms can be unambiguously characterized by for instance their optical rotation in case "A" and "B" have an enantiomeric relationship. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction. In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1" and "B1" and the second as "A2" and "B2", without further reference to the actual stereochemical configuration.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

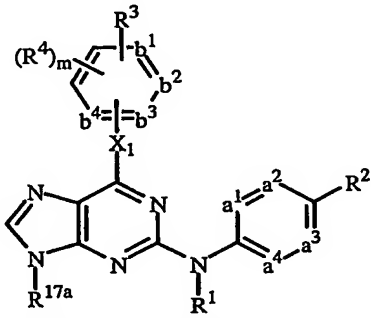
Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their salts, their quaternary amines and their stereochemically isomeric forms. Of special interest are those compounds of formula (I) which are stereochemically pure.

Whenever used hereinbefore or hereinafter that substituents can be selected each independently out of a list of numerous definitions, such as for example for R^9 and R^{10}, all possible combinations are intended which are chemically possible and which lead to chemically stable molecules.

A particular group of compounds are those compounds of formula (I) wherein $-a^1=a^2-C(R^2)=a^3-a^4=$ represents a bivalent radical of formula -CH=CH-C(R^2)=CH-CH= (a-1); $-b^1=b^2-b^3=b^4-$ represents a bivalent radical of formula -CH=CH-CH=CH- (b-1); -A-B- represents a bivalent radical of formula $-N=CH-NR^{17}-$ (c-1) or $-NR^{17}-CH=N-$ (c-2); m is 2; R^1 is hydrogen; R^2 is cyano, aminocarbonyl or C_{1-6}alkyl, in particular cyano or C_{1-6}alkyl; X_1 is $-NR^5-$ or -O-; R^3 is cyano; C_{1-6}alkyl; C_{1-6}alkyl substituted with cyano; C_{1-6}alkyloxy optionally substituted with cyano; C_{2-6}alkenyl substituted with cyano or $-C(=O)-NR^9R^{10}$; each R^4 independently is halo, C_{1-6}alkyl or C_{1-6}alkyloxy; R^5 is hydrogen; R^9 and R^{10} each independently are hydrogen or C_{1-6}alkyl; or R^9 and R^{10} may be taken together to form a bivalent radical of

formula $-CH_2-CH_2-O-CH_2-CH_2-$ (d-3); R^{17} is hydrogen or C_{1-6}alkyl substituted with aryl; aryl is phenyl substituted with C_{1-6}alkyloxy.

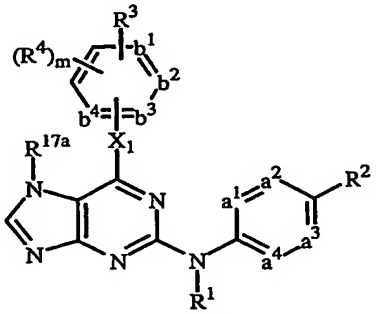
Also an interesting group of compounds are those compounds of formula (I) having the formula



(I-a)

the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines or the stereochemically isomeric forms thereof, wherein
$-a^1=a^2-C(R^2)=a^3-a^4=$; $-b^1=b^2-b^3=b^4-$; m; X_1; R^1; R^2; R^3; R^4 are as defined for the compounds of formula (I); R^{17a} is C_{1-6}alkyl or C_{1-6}alkyl substituted with aryl.

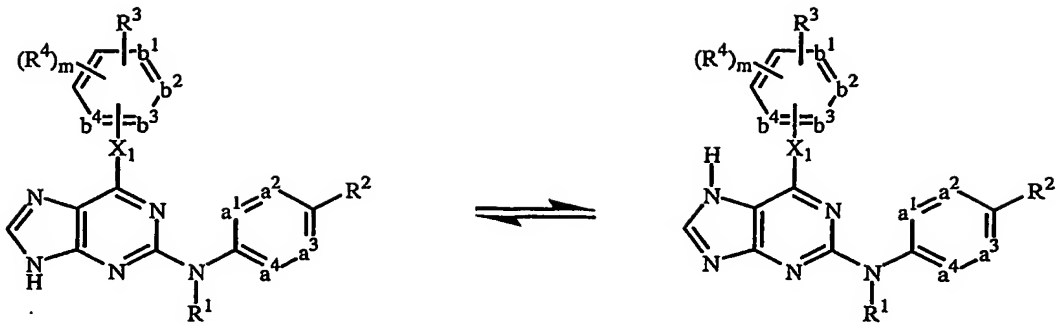
Another interesting group of compounds are those compounds of formula (I) having the formula



(I-b)

the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines or the stereochemically isomeric forms thereof, wherein
$-a^1=a^2-C(R^2)=a^3-a^4=$; $-b^1=b^2-b^3=b^4-$; m; X_1; R^1; R^2; R^3; R^4 are as defined for the compounds of formula (I); R^{17a} is C_{1-6}alkyl or C_{1-6}alkyl substituted with aryl.

Yet a further interesting group of compounds are those compounds of formula (I) having the formula



(I-c) (I-d)

the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines or the stereochemically isomeric forms thereof, wherein
$-a^1=a^2-C(R^2)=a^3-a^4=$; $-b^1=b^2-b^3=b^4-$; m; X_1; R^1; R^2; R^3; R^4 are as defined for the compounds of formula (I).

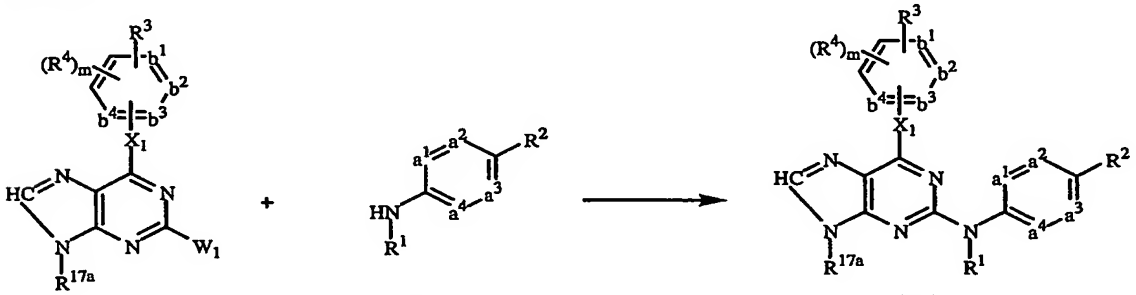
Particular interesting compounds of formula (I-a), (I-b), (I-c) or (I-d), the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines or the stereochemically isomeric forms thereof, are those compounds wherein $-a^1=a^2-C(R^2)=a^3-a^4=$ represents a bivalent radical of formula -CH=CH-C(R^2)=CH-CH= (a-1); $-b^1=b^2-b^3=b^4-$ represents a bivalent radical of formula -CH=CH-CH=CH- (b-1); m is 2; R^1 is hydrogen; R^2 is cyano, aminocarbonyl or C_{1-6}alkyl, in particular cyano or C_{1-6}alkyl; X_1 is $-NR^5-$ or -O-; R^3 is cyano; C_{1-6}alkyl; C_{1-6}alkyl substituted with cyano; C_{1-6}alkyloxy optionally substituted with cyano; C_{2-6}alkenyl substituted with cyano or $-C(=O)-NR^9R^{10}$; each R^4 independently is halo, C_{1-6}alkyl or C_{1-6}alkyloxy; R^5 is hydrogen; R^9 and R^{10} each independently are hydrogen; C_{1-6}alkyl; or R^9 and R^{10} may be taken together to form a bivalent radical of formula $-CH_2-CH_2-O-CH_2-CH_2-$ (d-3); R^{17a} is C_{1-6}alkyl substituted with aryl; aryl is phenyl substituted with C_{1-6}alkyloxy.

Further interesting compounds are those compounds of formula (I), (I-a), (I-b), (I-c) or (I-d), wherein one or more, preferably all, of the following definitions apply :
a) R^1 is hydrogen;
b) R^2 is cyano or aminocarbonyl, in particular cyano;
c) R^3 is C_{2-6}alkenyl substituted with cyano; C_{1-6}alkyloxy substituted with cyano; C_{1-6}alkyloxy; cyano; C_{1-6}alkyl;
d) R^4 is C_{1-6}alkyl, halo, C_{1-6}alkyloxy;
e) X_1 is NH or O;

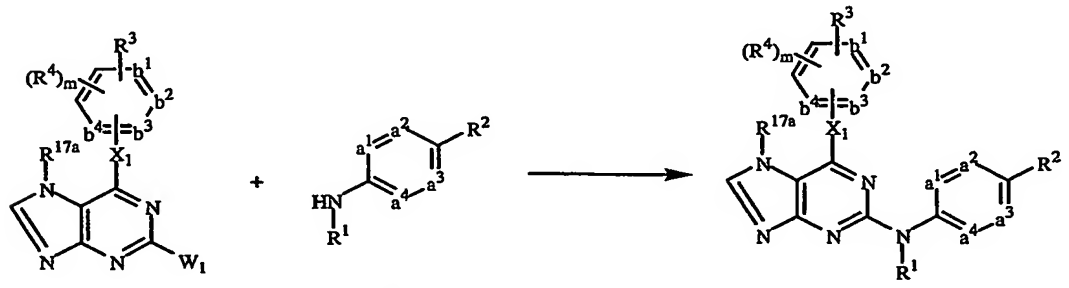
f) -a^1=a^2-C(R^2)=a^3-a^4= is a bivalent radical of formula -CH=CH-C(R^2)=CH-CH= (a-1);
g) -b^1=b^2-b^3=b^4- is a bivalent radical of formula -CH=CH-CH=CH- (b-1);
h) m is 2.

Preferred compounds of formula (I), (I-a), (I-b), (I-c) or (I-d), are compounds 28, 26, 19, 24, 4, 33, 34, 29, 30, 2, 6, 31 and 14 (see Tables 1, 2 and 3), their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms thereof.

In general, compounds of formula (I) wherein R^{17} is other than hydrogen, said R^{17} being represented by R^{17a}, and said compounds being represented by formula (I-a) or (I-b), can be prepared by reacting an intermediate of formula (II-a) or (II-b) wherein W_1 represents a suitable leaving group, such as for example halogen, e.g. chloro and the like, with an intermediate of formula (III) in the presence of a suitable catalyst, such as for example $Pd(OAc)_2$, $Pd_2(dba)_3$ and the like, a suitable ligand, such as for example a mixture of (+) and (-) 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, a suitable base, such as for example Cs_2CO_3 or Na_3PO_4, and a suitable solvent, such as for example toluene.



(II-a) (III) (I-a)



(II-b) (III) (I-b)

The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. tert.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

For instance, a compound of formula (I) wherein R^3 comprises cyano, can be converted into a compound of formula (I) wherein R^3 comprises aminocarbonyl, by reaction with HCOOH, in the presence of a suitable acid, such as hydrochloric acid. A compound of formula (I) wherein R^3 comprises cyano, can also further be converted into a compound of formula (I) wherein R^3 comprises tetrazolyl, by reaction with sodium azide in the presence of ammonium chloride and *N*, *N* -dimethylacetamide.

Compounds of formula (I) wherein R^3 comprises aminocarbonyl, can be converted into a compound of formula (I) wherein R^3 comprises cyano, in the presence of a suitable dehydrating agent. The dehydration can be performed according to methodologies well-known to the person skilled in the art, such as the ones disclosed in "Comprehensive Organic Transformations. A guide to functional group preparations" by Richard C. Larock, John Wiley & Sons, Inc, 1999, p 1983-1985, which is incorporated herein by reference. Different suitable reagents are enumerated in said reference, such as for example $SOCl_2$, $HOSO_2NH_2$, $ClSO_2NCO$, $MeO_2CNSO_2NEt_3$, $PhSO_2Cl$, TsCl, P_2O_5, $(Ph_3PO_3SCF_3)O_3SCF_3$, polyphosphate ester, $(EtO)_2POP(OEt)_2$, $(EtO)_3PI_2$, 2-chloro-1,3,2-dioxaphospholane, 2,2,2-trichloro-2,2-dihydro-1,3,2-dioxaphospholane, $POCl_3$, PPh_3, $P(NCl_2)_3$, $P(NEt_2)_3$,$COCl_2$, $NaCl.AlCl_3$, ClCOCOCl, $ClCO_2Me$, Cl_3CCOCl, $(CF_3CO)_2O$, $Cl_3CN{=}CCl_2$, 2,4,6-trichloro-1,3,5-triazine, $NaCl.AlCl_3$, $HN(SiMe_2)_3$, $N(SiMe_2)_4$, $LiAlH_4$ and the like. All the reagents listed in said publication are incorporated herein by reference.

Compounds of formula (I) wherein R^3 comprises C_{2-6}alkenyl can be converted into a compound of formula (I) wherein R^3 comprises C_{1-6}alkyl by reduction in the presence of a suitable reducing agent, such as for example H_2, in the presence of a suitable catalyst, such as for example palladium on charcoal, and in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol.

Compounds of formula (I) wherein R^3 represents CH(OH)-R^{16},can be converted into a compound of formula (I) wherein R^3 represents C(=O)-R^{16} by reaction with Jones's reagent in the presence of a suitable solvent, such as for example 2-propanone.

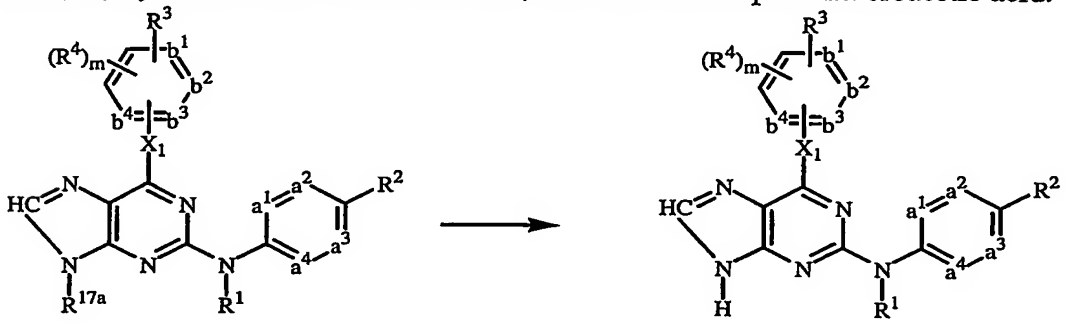
Compound of formula (I) wherein R^3 represents C(=O)-CH_2-R^{16a}, wherein R^{16a} represents cyano, aminocarbonyl or mono –or di(C_{1-4}alkyl)aminocarbonyl, can be converted into a compound of formula (I) wherein R^3 represents C(Cl)=CH-R^{16a} by reaction with $POCl_3$.

Compounds of formula (I) wherein R^3 represents a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle substituted with formyl can be converted into compounds of formula (I) wherein R^3 represents a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle substituted with CH(=N-O-R^8) by reaction with NH_2OR^8 in the presence of a suitable base, such as for example sodium hydroxide and a suitable solvent, such as for example an alcohol, e.g. ethanol and the like. Compounds of formula (I) wherein R^3 represents a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle substituted with CH(=N-O-R^8) can be converted into a compound of formula (I) wherein R^3 represents a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle substituted with CN by reaction with a carbodiimide in the presence of a suitable solvent, such as for example tetrahydrofuran.

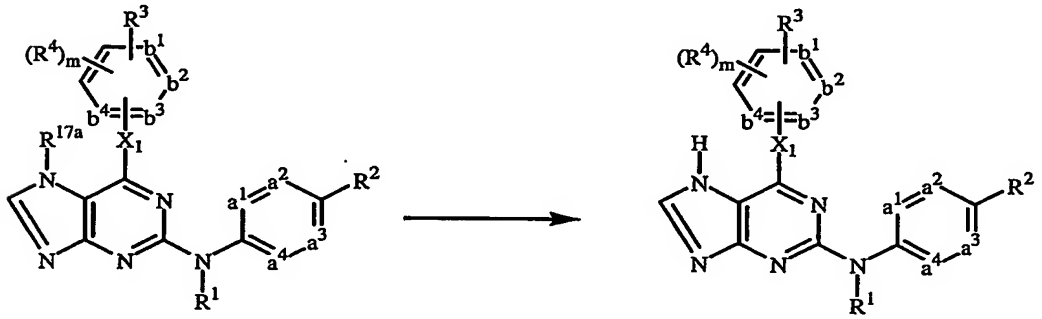
Compounds of formula (I) wherein R^4 represents nitro, can be converted into a compound of formula (I) wherein R^4 is amino, in the presence of a suitable reducing agent, such as for example H_2, in the presence of a suitable catalyst, such as for example Raney Nickel, and in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol.

Compounds of formula (I) wherein R^1 is hydrogen, can be converted into a compound of formula (I) wherein R^1 is C_{1-6}alkyl, by reaction with a suitable alkylating agent, such as for example iodo-C_{1-6}alkyl, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I-a) or (I-b) can be converted into a compound of formula (I) wherein R^{17} represents hydrogen, said compounds being represented by formula (I-c) and (I-d) by reaction with a suitable acid, such as for example trifluoroacetic acid.



(I-a) (I-c)



(I-b) (I-d)

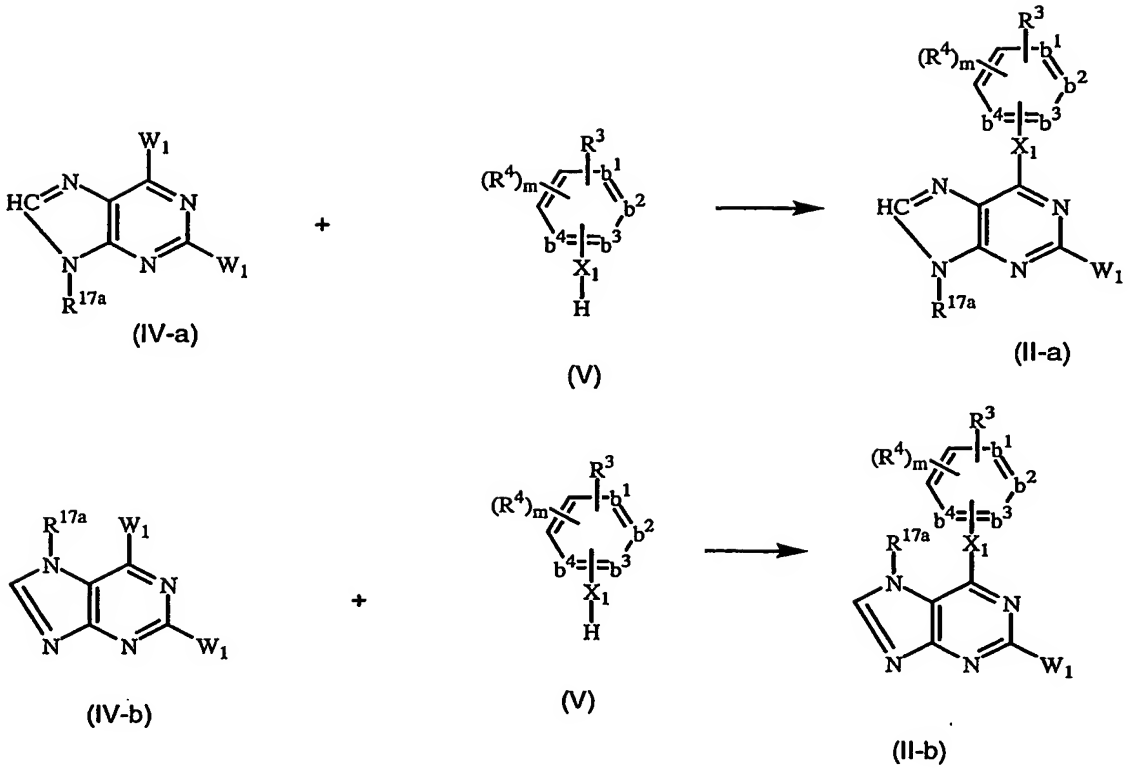
Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or

compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials are known compounds and may be commercially available or may be prepared according to art-known procedures or some of the compounds of formula (I) or the described intermediates may be prepared according to the procedures described in WO 99/50250 and WO 00/27825.

Intermediates of formula (II-a) or (II-b) can be prepared by reacting an intermediate of formula (IV) wherein W_1 is as defined above, with an intermediate of formula (V) in the presence of a suitable solvent, such as for example an alcohol, e.g. 2-butanol, a mixture of an alcohol and water, e.g. EtOH and water, or tetrahydrofuran, optionally in the presence of a suitable base, such as for example K_2CO_3, KO*tert*Bu.

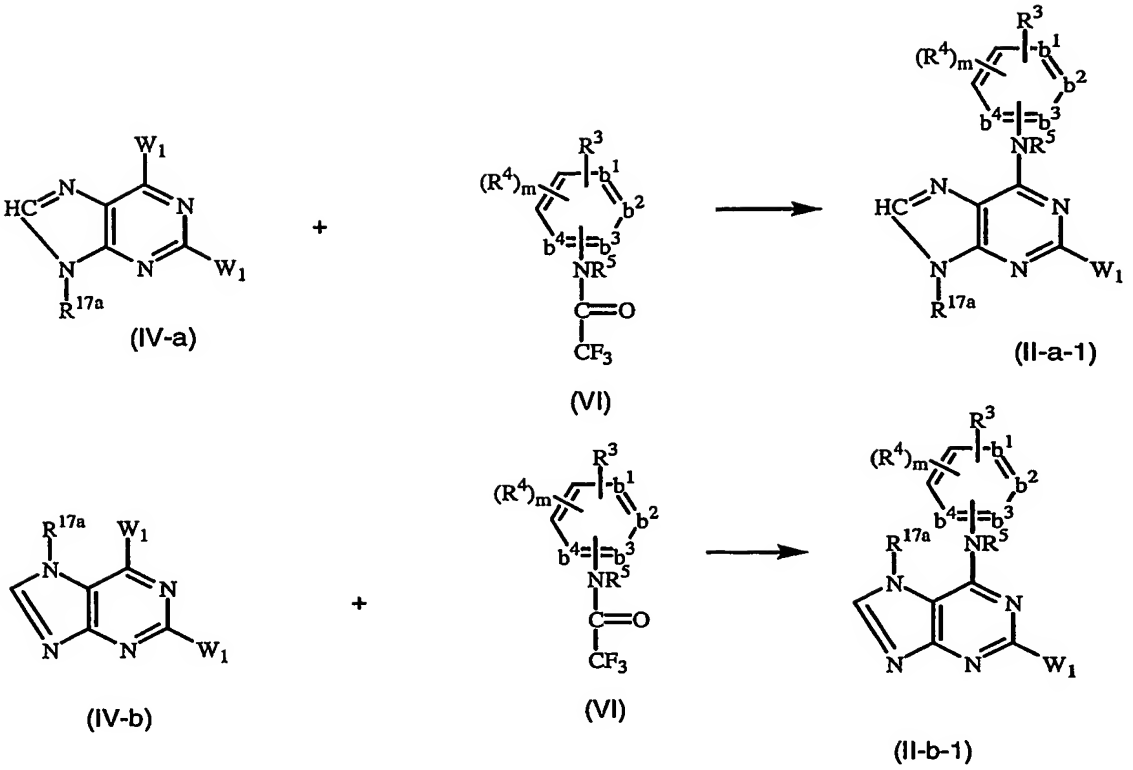


(IV-a) (V) (II-a)

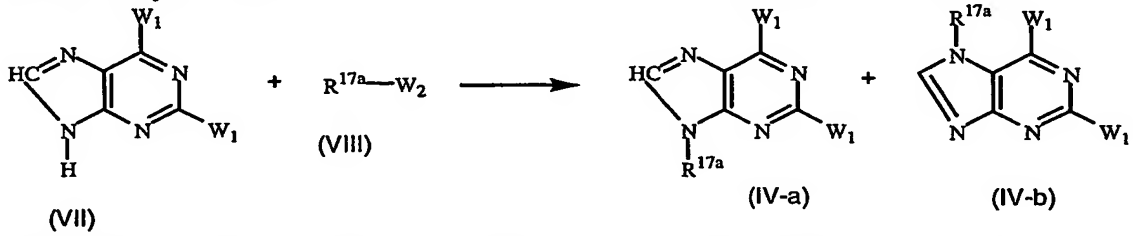
(IV-b) (V) (II-b)

Intermediates of formula (II-a) or (II-b) wherein R^3 represents C_{2-6}alkenyl substituted with aminocarbonyl, can be converted into an intermediate of formula (II-a) or (II-b) wherein R^3 represents C_{2-6}alkenyl substituted with cyano, in the presence of $POCl_3$.

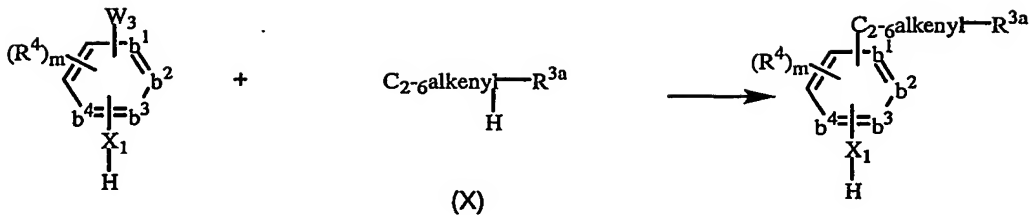
Intermediates of formula (II-a) and (II-b) wherein X_1 represents NR^5, said intermediates being represented by formula (II-a-1) and (II-b-1) can be prepared by reacting an intermediate of formula (IV-a) or (IV-b) with an intermediate of formula (VI) in the presence of a suitable solvent, such as for example tetrahydrofuran, t-amylOH or 1,2-dimethoxy ethane, and a suitable base, such as for example K_2CO_3.



Intermediates of formula (IV-a) and (IV-b) can be prepared by reacting an intermediate of formula (VII) wherein W_1 is as defined hereinabove, with an intermediate of formula (VIII) wherein W_2 represents a suitable leaving group, such as for example halogen, e.g. chloro and the like, in the presence of a suitable solvent, such as for example *N,N*-dimethylformamide, and a suitable base, such as for example K_2CO_3.

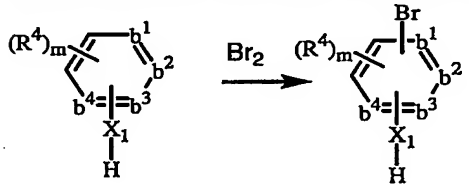


Intermediates of formula (V) wherein R^3 represents substituted C_{2-6}alkenyl, said intermediates being represented by C_{2-6}alkenyl-R^{3a} and said intermediates being represented by formula (V-a), can be prepared by reacting an intermediate of formula (IX) wherein W_3 represents a suitable leaving group, such as for example halogen, e.g. bromo and the like, with an intermediate of formula (X) in the presence of a suitable catalyst, such as for example $Pd(OAc)_2$, a suitable ligand, such as for example tris(2-methylphenyl)phosphine, a suitable base, such as for example *N,N*-diethylethanamine, and a suitable solvent, such as for example MeCN.



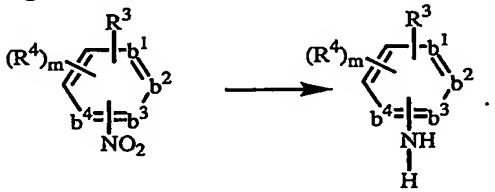
(IX) (X) (V-a)

Intermediates of formula (IX) wherein W_3 represents bromo, said intermediates being represented by formula (IX-a), can be prepared by reacting an intermediate of formula (XI) with Br_2 in the presence of a suitable acid, such as for example acetic acid, and a suitable solvent, such as an alcohol, e.g. methanol.



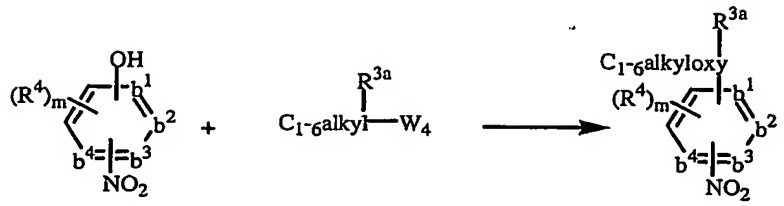
(XI) (IX-a)

Intermediates of formula (V) wherein X_1 represents NH, said intermediates being represented by formula (V-b), can be prepared by reducing an intermediate of formula (XII) in the presence of a suitable reducing agent, such as for example Fe, in the presence of NH_4Cl, and a suitable solvent, such as for example alcohol/water mixture, e.g. $MeOH/H_2O$ (1:2).



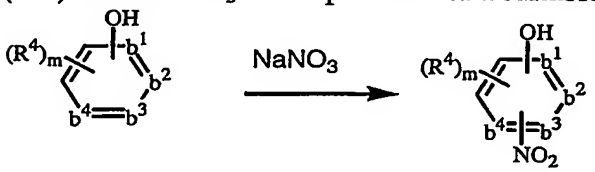
(XII) (V-b)

Intermediates of formula (XII) wherein R^3 represents substituted C_{1-6}alkyloxy, said R^3 being represented by R^{3a}-C_{1-6}alkyloxy, and said intermediates being represented by formula (XII-a), can be prepared by reacting an intermediate of formula (XIII) with an intermediate of formula (XIV) wherein W_4 represents a suitable leaving group, such as for example halogen, e.g. chloro and the like, in the presence of a suitable base, such as NaI, K_2CO_3, and a suitable solvent, such as for example acetone.



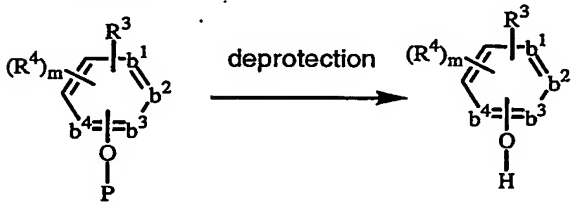
(XIII) (XIV) (XII-a)

Intermediates of formula (XIII) can be prepared by reacting an intermediate of formula (XV) with $NaNO_3$ in the presence of a suitable solvent, such as for example $MeSO_3H$.



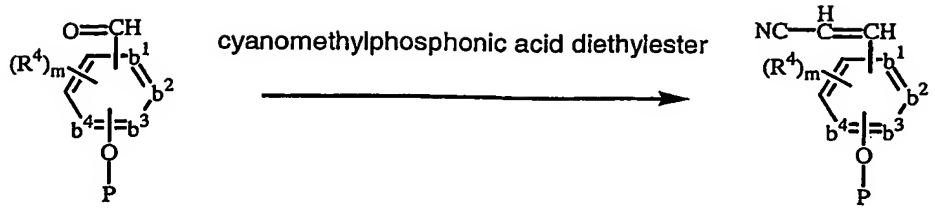
(XV) (XIII)

Intermediates of formula (V) wherein X_1 represents O, said intermediates being represented by formula (V-c), can be prepared by deprotecting an intermediate of formula (XVI) wherein P represents a suitable protecting group, such as for example $-Si(CH_3)_2C(CH_3)_3$ or those protecting groups mentioned in Chapter 7 of 'Protective Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991), in the presence of 4-methylbenzenesulfonic acid and a suitable solvent, such as for example an alcohol, e.g. methanol.



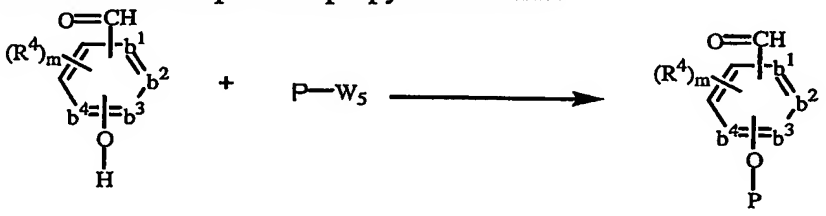
(XVI) (V-c)

Intermediates of formula (XVI) wherein R^3 represents cyanovinyl, said intermediates being represented by formula (XVI-a), can be prepared by reacting an intermediate of formula (XVII) with cyanomethylphosphonic acid diethylester in the presence of a suitable alcoholate, such as for example sodium methanolate, and a suitable solvent, such as for example tetrahydrofuran.



(XVII) (XVI-a)

Intermediates of formula (XVII) can be prepared by reacting an intermediate of formula (XVIII) with an intermediate of formula (XIX) wherein W_5 represents a suitable leaving group, such as for example halogen, e.g. chloro and the like, in the presence of a suitable solvent, such as for example *N,N*-dimethylformamide , and a suitable base, such as for example diisopropylethanamine.

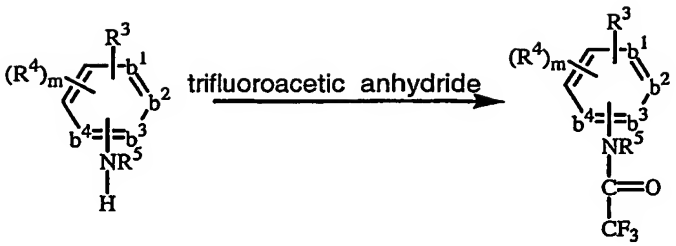


(XVIII) (XIX) (XVII)

Intermediates of formula (V-b) wherein R^3 represents C_{2-6}alkenyl-C(=O)-NH_2, can be converted into an intermediate of formula (V-b) wherein R^3 represents C_{2-6}alkenyl-CN by reaction with $POCl_3$, optionally in the presence of dichloromethane.

Intermediates of formula (V) wherein R^3 represents C_{2-6}alkenyl-CN, can be converted into an intermediate of formula (V) wherein R^3 represents C_{1-6}alkyl-CN by reaction with H_2, in the presence of a suitable catalyst, such as for example palladium on charcoal, and in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol.

Intermediates of formula (VI) can be prepared by reacting an intermediate of formula (XX) with trifluoroacetic anhydride in the presence of a suitable solvent, such as for example 1,2-dimethoxy ethane.



(XX) (VI)

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized as a mixture of stereoisomeric forms, in particular in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds may need to be blocked by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), benzyl and tetrahydropyranyl. Suitable protecting groups for amino include *tert*-butyloxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C_{1-6}alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after a reaction step.

The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis' 2nd edition, T W Greene & P G M Wutz, Wiley Interscience (1991).

The compounds of formula (I), (I-a), (I-b), (I-c) and (I-d) show antiretroviral properties (reverse transcriptase inhibiting properties), in particular against Human Immunodeficiency Virus (HIV), which is the aetiological agent of Acquired Immune Deficiency Syndrome (AIDS) in humans. The HIV virus preferentially infects human T-4 cells and destroys them or changes their normal function, particularly the coordination of the immune system. As a result, an infected patient has an ever decreasing number of T-4 cells, which moreover behave abnormally. Hence, the immunological defense system is unable to combat infections and neoplasms and the HIV infected subject usually dies by opportunistic infections such as pneumonia, or by cancers. Other conditions associated with HIV infection include thrombocytopaenia, Kaposi's sarcoma and infection of the central nervous system characterized by progressive demyelination, resulting in dementia and symptoms such as, progressive dysarthria, ataxia and disorientation. HIV infection further has also been associated with peripheral neuropathy, progressive generalized lymphadenopathy (PGL) and AIDS-related complex (ARC).

The present compounds also show activity against (multi) drug resistant HIV strains, in particular (multi) drug resistant HIV-1 strains, more in particular the present compounds show activity against HIV strains, especially HIV-1 strains, that have acquired resistance to one or more art-known non-nucleoside reverse transcriptase inhibitors. Art-known non-nucleoside reverse transcriptase inhibitors are those non-nucleoside reverse transcriptase inhibitors other than the present compounds and in particular commercial non-nucleoside reverse transcriptase inhibitors. The present compounds also have little or no binding affinity to human α-1 acid glycoprotein; human α-1 acid glycoprotein does not or only weakly affect the anti HIV activity of the present compounds.

Due to their antiretroviral properties, particularly their anti-HIV properties, especially their anti-HIV-1-activity, the compounds of formula (I), (I-a), (I-b), (I-c) and (I-d), their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines or stereochemically isomeric forms thereof, are useful in the treatment of individuals infected by HIV and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals

infected with viruses whose existence is mediated by, or depends upon, the enzyme reverse transcriptase. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HIV and other pathogenic retroviruses, include AIDS, AIDS-related complex (ARC), progressive generalized lymphadenopathy (PGL), as well as chronic Central Nervous System diseases caused by retroviruses, such as, for example HIV mediated dementia and multiple sclerosis.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines against above-mentioned conditions. Said use as a medicine or method of treatment comprises the administration to HIV-infected subjects of an amount effective to combat the conditions associated with HIV and other pathogenic retroviruses, especially HIV-1. In particular, the compounds of formula (I), (I-a), (I-b), (I-c) and (I-d), their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines or stereochemically isomeric forms thereof, may be used in the manufacture of a medicament for the treatment or the prevention of HIV infections.

In view of the utility of the compounds of formula (I), (I-a), (I-b), (I-c) and (I-d), there is provided a method of treating warm-blooded animals, including humans, suffering from or a method of preventing warm-blooded animals, including humans, to suffer from viral infections, especially HIV infections. Said method comprises the administration, preferably oral administration, of an effective amount of a compound of formula (I), (I-a), (I-b), (I-c) or (I-d), a *N*-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

The present invention also provides compositions for treating viral infections comprising a therapeutically effective amount of a compound of formula (I), (I-a), (I-b), (I-c) or (I-d), a *N*-oxide, pharmaceutically acceptable addition salt, quaternary amine or stereochemically isomeric form thereof, and a pharmaceutically acceptable carrier or diluent.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the

active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. The compounds of the present invention may also be administered via inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder. Any system developed for the delivery of solutions, suspensions or dry powders via oral or nasal inhalation or insufflation are suitable for the administration of the present compounds.

To aid solubility of the compounds of formula (I), (I-a), (I-b), (I-c) or (I-d), suitable ingredients, e.g. cyclodextrins, may be included in the compositions. Appropriate cyclodextrins are α-, β-, γ-cyclodextrins or ethers and mixed ethers thereof wherein one

or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxy-propyl or hydroxybutyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxy-ethyl; C_{1-6}alkylcarbonyl, particularly acetyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxypropyl-β-CD and (2-carboxy-methoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD (2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxy-propyl and hydroxyethyl.

The average molar substitution (M.*S*.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The average substitution degree (D.*S*.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The M.*S*. and D.*S*. value can be determined by various analytical techniques such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and infrared spectroscopy (IR). Depending on the technique used, slightly different values may be obtained for one given cyclodextrin derivative. Preferably, as measured by mass spectrometry, the M.*S*. ranges from 0.125 to 10 and the D.*S*. ranges from 0.125 to 3.

Other suitable compositions for oral or rectal administration comprise particles consisting of a solid dispersion comprising a compound of formula (I), (I-a), (I-b), (I-c) or (I-d) and one or more appropriate pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" used hereinafter defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, in casu the compound of formula (I), (I-a), (I-b), (I-c) or (I-d) and the water-soluble polymer, wherein one component is dispersed more or less evenly throughout the other component or components (in case additional pharmaceutically acceptable formulating agents, generally known in the art, are included, such as plasticizers, preservatives and the like). When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermo-dynamics, such a solid dispersion will be called "a solid solution". Solid solutions are preferred physical systems because the components therein are usually

readily bioavailable to the organisms to which they are administered. This advantage can probably be explained by the ease with which said solid solutions can form liquid solutions when contacted with a liquid medium such as the gastro-intestinal juices. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid solution is less than that required for the dissolution of components from a crystalline or microcrystalline solid phase.

The term "a solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase. For example, the term "a solid dispersion" also relates to a system having domains or small regions wherein amorphous, microcrystalline or crystalline compound of formula (I), (I-a), (I-b), (I-c) or (I-d), or amorphous, microcrystalline or crystalline water-soluble polymer, or both, are dispersed more or less evenly in another phase comprising water-soluble polymer, or compound of formula (I), (I-a), (I-b), (I-c) or (I-d), or a solid solution comprising compound of formula (I), (I-a), (I-b), (I-c) or (I-d) and water-soluble polymer. Said domains are regions within the solid dispersion distinctively marked by some physical feature, small in size, and evenly and randomly distributed throughout the solid dispersion.

Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation.

The solution-evaporation process comprises the following steps :

a) dissolving the compound of formula (I), (I-a), (I-b), (I-c) or (I-d) and the water-soluble polymer in an appropriate solvent, optionally at elevated temperatures;

b) heating the solution resulting under point a), optionally under vacuum, until the solvent is evaporated. The solution may also be poured onto a large surface so as to form a thin film, and evaporating the solvent therefrom.

In the spray-drying technique, the two components are also dissolved in an appropriate solvent and the resulting solution is then sprayed through the nozzle of a spray dryer followed by evaporating the solvent from the resulting droplets at elevated temperatures.

The preferred technique for preparing solid dispersions is the melt-extrusion process comprising the following steps :

a) mixing a compound of formula (I), (I-a), (I-b), (I-c) or (I-d) and an appropriate water-soluble polymer,
b) optionally blending additives with the thus obtained mixture,
c) heating and compounding the thus obtained blend until one obtains a homogenous melt,
d) forcing the thus obtained melt through one or more nozzles; and
e) cooling the melt till it solidifies.

The terms "melt" and "melting" should be interpreted broadly. These terms not only mean the alteration from a solid state to a liquid state, but can also refer to a transition to a glassy state or a rubbery state, and in which it is possible for one component of the mixture to get embedded more or less homogeneously into the other. In particular cases, one component will melt and the other component(s) will dissolve in the melt thus forming a solution, which upon cooling may form a solid solution having advantageous dissolution properties.

After preparing the solid dispersions as described hereinabove, the obtained products can be optionally milled and sieved.

The solid dispersion product may be milled or ground to particles having a particle size of less than 600 μm, preferably less than 400 μm and most preferably less than 125 μm.

The particles prepared as described hereinabove can then be formulated by conventional techniques into pharmaceutical dosage forms such as tablets and capsules.

It will be appreciated that a person of skill in the art will be able to optimize the parameters of the solid dispersion preparation techniques described above, such as the most appropriate solvent, the working temperature, the kind of apparatus being used, the rate of spray-drying, the throughput rate in the melt-extruder

The water-soluble polymers in the particles are polymers that have an apparent viscosity, when dissolved at 20°C in an aqueous solution at 2 % (w/v), of 1 to 5000 mPa.s more preferably of 1 to 700 mPa.s, and most preferred of 1 to 100 mPa.s. For example, suitable water-soluble polymers include alkylcelluloses, hydroxyalkylcelluloses, hydroxyalkyl alkylcelluloses, carboxyalkylcelluloses, alkali metal salts of carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters, starches, pectines, chitin derivates, di-, oligo- and polysaccharides such as trehalose,

alginic acid or alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi, polyacrylic acids and the salts thereof, polymethacrylic acids and the salts thereof, methacrylate copolymers, polyvinylalcohol, polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate, combinations of polyvinylalcohol and polyvinylpyrrolidone, polyalkylene oxides and copolymers of ethylene oxide and propylene oxide. Preferred water-soluble polymers are hydroxypropyl methylcelluloses.

Also one or more cyclodextrins can be used as water soluble polymer in the preparation of the above-mentioned particles as is disclosed in WO 97/18839. Said cyclodextrins include the pharmaceutically acceptable unsubstituted and substituted cyclodextrins known in the art, more particularly α, β or γ cyclodextrins or the pharmaceutically acceptable derivatives thereof.

Substituted cyclodextrins which can be used to prepare the above described particles include polyethers described in U.S. Patent 3,459,731. Further substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}alkyl, hydroxyC_{1-6}alkyl, carboxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonylC_{1-6}alkyl or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}alkyl, hydroxyC_{2-4}alkyl or carboxyC_{1-2}alkyl or more in particular by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxy-methyl or carboxyethyl.

Of particular utility are the β-cyclodextrin ethers, e.g. dimethyl-β-cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and polyethers, e.g. hydroxypropyl β-cyclodextrin and hydroxyethyl β-cyclodextrin, being examples. Such an alkyl ether may be a methyl ether with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example be formed from the reaction between β-cyclodextrin an propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

Another type of substituted cyclodextrins is sulfobutylcyclodextrines.

The ratio of the compound of formula (I), (I-a), (I-b), (I-c) or (I-d) over the water soluble polymer may vary widely. For example ratios of 1/100 to 100/1 may be

applied. Interesting ratios of the compound of formula (I), (I-a), (I-b), (I-c) or (I-d) over cyclodextrin range from about 1/10 to 10/1. More interesting ratios range from about 1/5 to 5/1.

It may further be convenient to formulate the compounds of formula (I), (I-a), (I-b), (I-c) or (I-d) in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Useful surface modifiers are believed to include those which physically adhere to the surface of the compound of formula (I) but do not chemically bond to said compound.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the compounds of formula (I), (I-a), (I-b), (I-c) or (I-d) involves a pharmaceutical composition whereby the compounds of formula (I), (I-a), (I-b), (I-c) or (I-d) are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration.

Said beads comprise a central, rounded or spherical core, a coating film of a hydrophilic polymer and a compound of formula (I), (I-a), (I-b), (I-c) or (I-d) and optionally a seal-coating layer.

Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical

carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Those of skill in the treatment of HIV-infection could determine the effective daily amount from the test results presented here. In general it is contemplated that an effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I), (I-a), (I-b), (I-c) or (I-d) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines and are not intended to limit the scope or use of the invention to any extent.

The present compounds of formula (I), (I-a), (I-b), (I-c) or (I-d) can be used alone or in combination with other therapeutic agents, such as anti-virals, antibiotics, immunomodulators or vaccines for the treatment of viral infections. They may also be used alone or in combination with other prophylactic agents for the prevention of viral infections. The present compounds may be used in vaccines and methods for protecting individuals against viral infections over an extended period of time. The compounds may be employed in such vaccines either alone or together with other compounds of this invention or together with other anti-viral agents in a manner consistent with the conventional utilization of reverse transcriptase inhibitors in vaccines. Thus, the present compounds may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period of time against HIV infection.

Also, the combination of an antiretroviral compound and a compound of formula (I), (I-a), (I-b), (I-c) or (I-d) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), (I-a), (I-b), (I-c) or (I-d), and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. Said other antiretroviral compounds may be known antiretroviral compounds such as suramine, pentamidine, thymopentin, castanospermine, dextran (dextran sulfate), foscarnet-sodium (trisodium phosphono formate); nucleoside reverse transcriptase inhibitors, e.g. zidovudine (3'-azido-3'-deoxythymidine, AZT), didanosine (2',3'-dideoxyinosine; ddI), zalcitabine (dideoxycytidine, ddC) or lamivudine (2'-3'-dideoxy-3'-thiacytidine, 3TC), stavudine (2',3'-didehydro-3'-deoxythymidine, d4T), abacavir and the like; non-nucleoside reverse transcriptase inhibitors such as nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido-[3,2-b : 2',3'-e][1,4]diazepin-6-one), efavirenz, delavirdine, TMC-120, TMC-125 and the like; phosphonate reverse transcriptase inhibitors, e.g. tenofovir and the like; compounds of the TIBO (tetrahydro-imidazo[4,5,1-jk][1,4]-benzodiazepine-2(1*H*)-one and thione)-type e.g. (S)-8-chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo-[4,5,1-jk][1,4]benzodiazepine-2(1*H*)-thione; compounds of the α-APA (α-anilino phenyl acetamide) type e.g. α-[(2-nitrophenyl)amino]-2,6-dichlorobenzene-acetamide and the like; inhibitors of trans-activating proteins, such as TAT-inhibitors, e.g. RO-5-3335, or REV inhibitors, and the like; protease inhibitors *e.g.* indinavir, ritonavir, saquinavir, lopinavir (ABT-378), nelfinavir, amprenavir, TMC-126, BMS-232632, VX-175 and the like; fusion inhibitors, e.g. T-20, T-1249 and the like; CXCR4 receptor antagonists, e.g. AMD-3100 and the like; inhibitors of the viral integrase; nucleotide-like reverse transcriptase inhibitors, e.g. tenofovir and the like; ribonucleotide reductase inhibitors, e.g. hydroxyurea and the like.

By administering the compounds of the present invention with other anti-viral agents which target different events in the viral life cycle, the therapeutic effect of these compounds can be potentiated. Combination therapies as described above exert a synergistic effect in inhibiting HIV replication because each component of the combination acts on a different site of HIV replication. The use of such combinations may reduce the dosage of a given conventional anti-retroviral agent which would be required for a desired therapeutic or prophylactic effect as compared to when that agent is administered as a monotherapy. These combinations may reduce or eliminate the

side effects of conventional single anti-retroviral therapy while not interfering with the anti-viral activity of the agents. These combinations reduce potential of resistance to single agent therapies, while minimizing any associated toxicity. These combinations may also increase the efficacy of the conventional agent without increasing the associated toxicity.

The compounds of the present invention may also be administered in combination with immunomodulating agents, e.g. levamisole, bropirimine, anti-human alpha interferon antibody, interferon alpha, interleukin 2, methionine enkephalin, diethyldithiocarbamate, tumor necrosis factor, naltrexone and the like; antibiotics, e.g. pentamidine isethiorate and the like; cholinergic agents, e.g. tacrine, rivastigmine, donepezil, galantamine and the like; NMDA channel blockers, e.g. memantine to prevent or combat infection and diseases or symptoms of diseases associated with HIV infections, such as AIDS and ARC, e.g. dementia. A compound of formula (I), (I-a), (I-b), (I-c) or (I-d) can also be combined with another compound of formula (I), (I-a), (I-b), (I-c) or (I-d).

Although the present invention focuses on the use of the present compounds for preventing or treating HIV infections, the present compounds may also be used as inhibitory agents for other viruses which depend on similar reverse transcriptases for obligatory events in their life cycle.

The following examples illustrate the present invention.

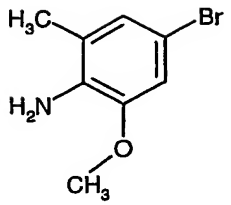
Experimental part

Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DME" is defined as 1,2-dimethoxyethane, "DCM" is defined as dichloromethane, "THF" is defined as tetrahydrofuran, "BINAP" is defined as a mixture of (+) and (-) [1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine, "TFA" is defined as trifluoroacetic acid, "TFAA" is defined as trifluoroacetic anhydride, "DCE" is defined as 1,2-dichloro ethane and "DIPEA" is defined as diisopropylethanamine.

A. Preparation of the intermediate compounds

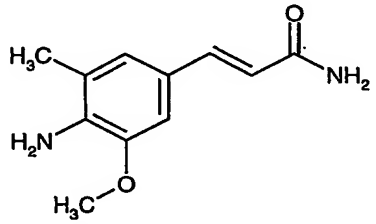
Example A1

a) Preparation of intermediate 1



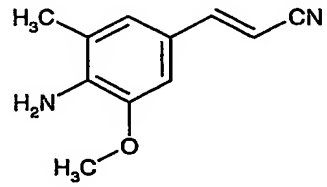
2-Methoxy-6-methylbenzenamine (12.12 g) was dissolved in 100 ml of MeOH and 10 ml of HOAc. Temperature was lowered to 0°C. A solution of 14.12 g Br_2 in 50 ml of MeOH was added with carefull temperature-control. After addition, the solvents were evaporated and the residue was dissolved in 300 ml of diethyl ether and 100 ml of 2M NaOH. The layers were separated. The ether-layer was dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. Yield: 18.68 g of intermediate 1 (4-bromo-2-methoxy-6-methylbenzenamine) (98%) .

b) Preparation of intermediate 2



0.1 eq of $Pd(OAc)_2$ (1.23 g), 0.3 eq of tris(2-methylphenyl)phosphine (5.0 g), 1.5 eq of Et_3N (8.31 g), 4-bromo-2-methoxy-6-methylbenzenamine (intermediate 1) (11.83 g) and 2-propenamide (1.5 eq., 5.84 g) were brought in 150 ml of MeCN and N_2 was bubbled through the suspension for at least 20 minutes. Then a cooler was mounted strictly under nitrogen atmosphere. The reaction was heated at 70°C overnight. The reaction mixture was allowed to cool to 20°C and was diluted with 700 ml of CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ (2x 100 ml) and dried with brine and Na_2SO_4. The residue was triturated in iPr_2O, filtered off and air-dried. Yield: 11.65 g of intermediate 2 (99%).

c) Preparation of intermediate 3

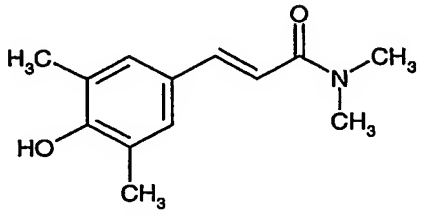


Intermediate 2 (11.65 g) was dissolved in 50 ml of $POCl_3$ at 20°C. The reaction mixture was stirred at 20°C and checked by TLC. The reaction mixture was added dropwise to 500 ml of diisopropyl ether. The precipitate was filtered off, the residu was added to 350 ml of EtOAc and 250 ml of $NaHCO_3$ (sat.). The layers were separated. The water-layer was washed with 150 ml of EtOAc once. The combined EtOAc-layers

were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. Yield: 9.55 g of intermediate 3 (85%).

Example A2

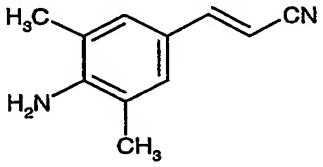
Preparation of intermediate 4

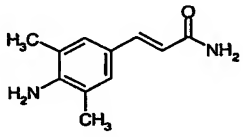


0.1 eq (335 mg) of $Pd(OAc)_2$, 0.2 eq (908 mg) of tris(2-methylphenyl)phosphine, 1.5 eq (3.11 ml) of Et_3N, 4-bromo-2,6-dimethylphenol (3.00 g) and *N,N*-dimethyl-2-propenamide (1.5 eq., 2.31 ml) were brought in 100 ml of MeCN and N_2 was bubbled through the suspension for at least 20 minutes. Then a cooler was mounted strictly under nitrogen atmosphere. The reaction was heated at 70°C overnight. The reaction mixture was allowed to cool to 20°C and was diluted with 500 ml of CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ (2x100 ml) and dried with brine and Na_2SO_4. The residue was sonicated in iPr_2O and filtered off. Yield: 2.26 g of intermediate 4 (69%).

Example A3

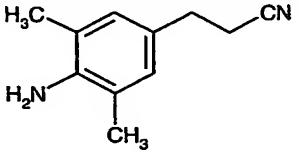
a) Preparation of intermediate 6





Intermediate 5 (prepared according to A1b) (6.81 g) was dissolved in 26 ml of $POCl_3$ at 20°C. The reaction mixture was stirred at 20°C and checked by TLC. The reaction mixture was added dropwise to 500 ml of diisopropyl ether. The precipitate was filtered off, the residu was added to 250 ml of EtOAc and 150 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The water-layer was washed with 100 ml of EtOAc once. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. Yield: 5.37 g of intermediate 6 (87%).

b) Preparation of intermediate 7

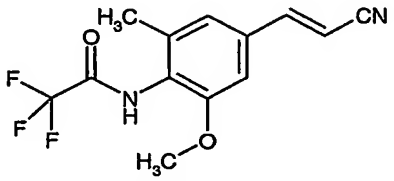


Hydrogenation at $P = P^0$ using 0.05 eq (0.88 g) of 5% Pd/C in 200 ml of EtOH with 1.40 gram of intermediate 6. After 4 hours, the Pd/C was filtered off and the filtrate was

evaporated and stripped with 50 ml of EtOAc and with 50 ml of DCM. Yield : 1.35 g of intermediate 7 (93%).

Example A4

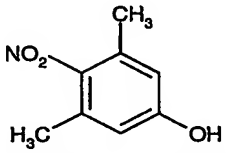
Preparation of intermediate 8



Intermediate 3 (3.81 g) was suspended in 100 ml of 1,2-dimethoxyethane (DME) at 0°C and stirred vigorously. At 0°C, a solution of TFAA (2.0 eq., 8.48 g) in DME was added dropwise. After vigorously stirring for 30 minutes at 0°C, the reaction mixture was stirred vigorously at 20°C and checked by TLC. The reaction was quenched by adding 400 ml of $NaHCO_3$ (sat.) (aq.). EtOAc (200 ml) was added to the quenched reaction mixture. The layers were separated. The water-layer was washed with EtOAc (100 ml) once. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. Yield : 5.77 g of intermediate 8 (98%).

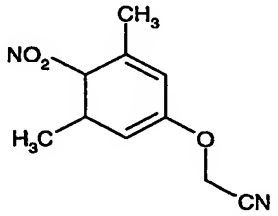
Example A5

a) Preparation of intermediate 9



3,5-Dimethylphenol (50 g) was dissolved in 200 ml of $MeSO_3H$ and cooled to 0°C. 1 eq (34.8 g) of $NaNO_3$ was added portion-whise at 0°C. After 18 hours, the reaction mixture was poured into 4 liter of ice-H_2O under vigorous stirring. The water was decanted. The residu was dissolved in 400 ml of EtOAc. The EtOAc extract was washed with sat. aq. $NaHCO_3$ (2x200 ml), dried using brine and Na_2SO_4, and purified using a mixture of EtOAc and n-heptane (4:1) on silicagel. Yield: 7.86 g of intermediate 9 (11%).

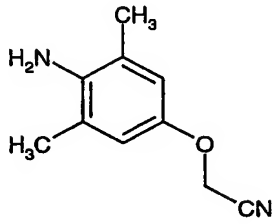
b) Preparation of intermediate 10



Intermediate 9 (1.40 g) was dissolved in 40 ml of acetone. Subsequently, K_2CO_3 (2.0 eq., 2.31 g) and NaI (0.1 eq., 126 mg) was added, followed by $ClCH_2CN$ (1.5 eq., 0.95 g). After completion of the reaction (GC), the reaction-mixture was filtered and concentrated. The residu was dissolved in 100 ml of EtOAc. The EtOAc extract was

washed with sat. aq. $NaHCO_3$ (2x200 ml), dried using brine and Na_2SO_4. Yield: 1.91 g of intermediate 10 (99%).

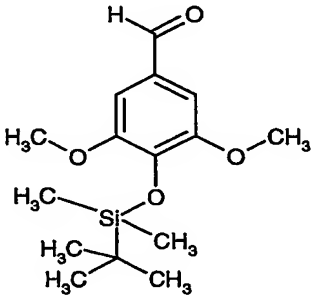
c) Preparation of intermediate 11



5 eq. (1.30 g) of NH_4Cl was dissolved in 20 ml of H_2O and 3 eq (0.81 g) of Fe was added. Intermediate 10 (1.00 g) was dissolved in 40 ml of MeOH. The solution was added to the aqueous solution. The reaction was stirred at 50°C and checked by TLC. The reaction-mixture was filtered hot. The filtrate was poured in 200 ml of EtOAc. The EtOAc extract was washed with sat. aq. $NaHCO_3$ (2x200 ml), dried using brine and Na_2SO_4. Yield : 0.92 g of intermediate 11 (100%).

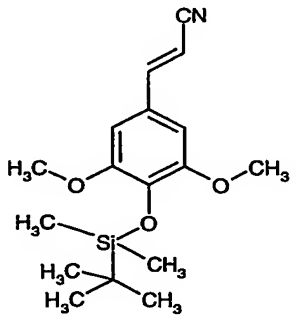
Example A6

a) Preparation of intermediate 12

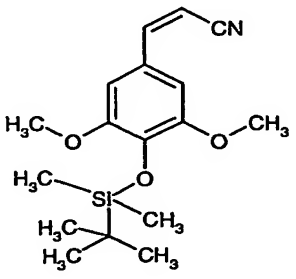


4-Hydroxy-3,5-dimethoxybenzaldehyde (2.00 g) and DIPEA (2.0 eq., 2.84 g) was dissolved in 25 ml of DMF. A solution of chloro(1,1-dimethylethyl)dimethylsilane (1.1 eq., 1.82 g) in 10 ml of DMF was added dropwise. After 18 hours, the reaction mixture was poured in 150 ml of water, followed by extraction with ethyl ether (2x100 ml). The organic layer was dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. Yield: 2.91 g of intermediate 12 (97%).

b) Preparation of intermediate 13 and 14



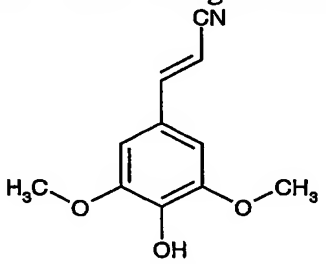
Intermediate 13



Intermediate 14

NaOMe (2.0 eq., 0.73 g) was suspended in 20 ml of THF. A solution of intermediate 12 (2.00 g) in 10 ml of THF was added dropwise. After stirring for 15 minutes, a solution of cyanomethylphosphonic acid diethyl ester (1.0 eq., 1.20 g) was added dropwise. After stirring for 18 hours, the reaction was quenched by adding 0.5 M HCl until the pH was below 1. The quenched reaction mixture was extracted with 150 ml of EtOAc. The layers were separated. The water-layer was washed with 50 ml of EtOAc once. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was dissolved in ethyl ether (50 ml). By adding heptane, the main product from the reaction (the trans-isomer, intermediate 13) precipitates. The mother liquer contains both the cis- and the trans-isomer. Yield : 0.58 g of intermediate 13 (27%).

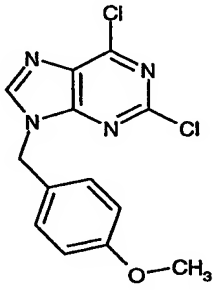
c) Preparation of intermediate 15



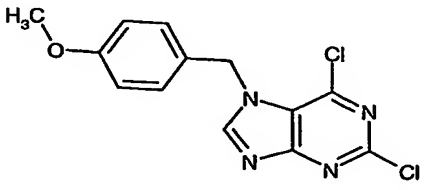
Intermediate 13 (580 mg) was dissolved in 15 ml of MeOH. TosOH (0.05 eq., 20 mg) was added. After 40 hours at 60°C, the deprotection was complete. The reaction-mixture was poured in 50 ml of water and extracted with 150 ml of EtOAc. The layers were separated. The water-layer was washed with 50 ml of EtOAc once. The combined EtOAc-layers were washed with 50 ml of $NaHCO_3$ (sat.) (aq.), dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. Yield : 0.33 g of intermediate 15 (89%).

Example A7

Preparation of intermediate 16 and 17



Intermediate 16



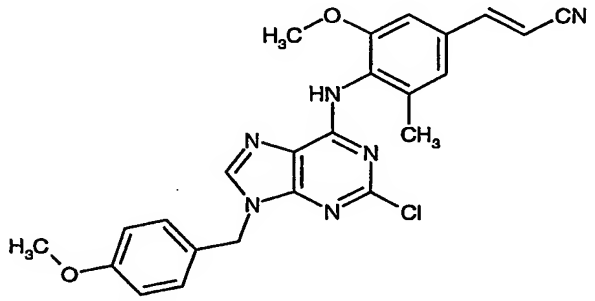
Intermediate 17

2,6-dichloro-1*H*-purine (18.32 g) and p-methoxybenzylchloride (1.0 eq., 15.72 g) were mixed with K_2CO_3 (1.0 eq, 15 g) in 100 ml of DMF. The reaction mixture was stirred vigorously and checked by TLC. The solvent was removed and the residu was dissolved in 500 ml of EtOAc and 0.1 M NaOH (100 ml). The layers were separated. The EtOAc-layer was washed with 0.1 M NaOH (2x100 ml), dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was purified by column

chromatography using n-heptane / EtOAc : 1 / 1 as the eluent. The first fraction yielded 14.39 g of intermediate 16, the second fraction yielded 8.54 g of intermediate 17.

Example A8

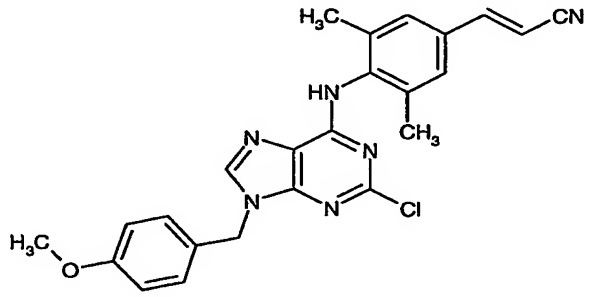
a) Preparation of intermediate 18

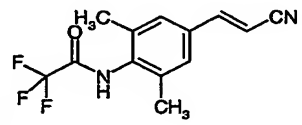


Intermediate 8 (prepared according to A4) (2.32 g) and intermediate 16 (prepared according to A7) (1.0 eq., 2.52 g) were mixed with K_2CO_3 (3.0 eq., 3.38 g) in 50 ml of DME . The reaction mixture was stirred vigorously at 80°C and checked by TLC and LC/MS. The organic solvents were removed and the residu was dissolved in 300 ml of EtOAc and 100 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The water-layer was washed with 100 ml of EtOAc once, subsequently two times with 150 ml of DCM. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The combined DCM-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and combined with the residu from the EtOAc-washings.

The residue was purified by trituration with 100 ml of ethanol. Yield : 2.69 g of intermediate 18 (72%).

b) Preparation of intermediate 20

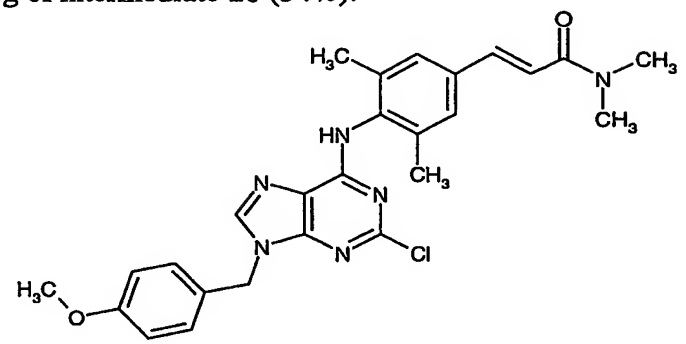


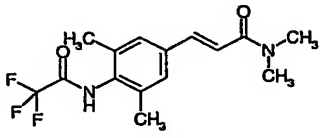


Intermediate 19 (1.0 eq.; 5.81 g) (prepared according to A4) and intermediate 16 (prepared according to A7) (1.0 eq, 2.52 g).) were mixed with K_2CO_3 (3.0 eq; 3.38 g)) in 100 ml of DME. The reaction mixture was stirred vigorously at 80°C and checked by TLC and LC/MS. The reaction mixture was dissolved in 400 ml of EtOAc and 100 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The water-layer was washed with 100 ml of EtOAc once. The combined EtOAc-layers were dried

(NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was purified by trituation with ethanol. Yield: 0.24 g of intermediate 20 (54%).

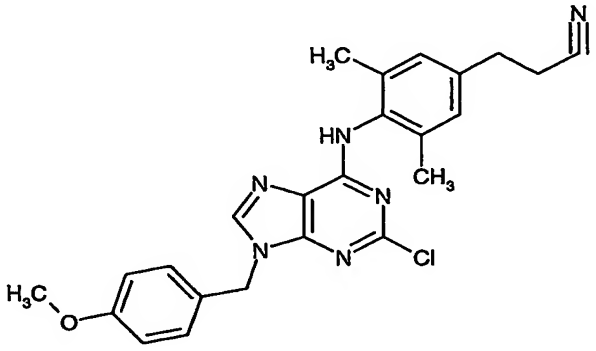
c) Preparation of intermediate 22



Intermediate 21  (1.0 eq.; 290 mg) (prepared according to A4) and intermediate 16 (prepared according to A7) (1.0 eq, 2.52 g).) were mixed with K_2CO_3 (3.0 eq; 3.38 g)) in 15 ml of t-amyl-OH. The reaction mixture was stirred vigorously at 80°C and checked by TLC and LC/MS. The organic solvents were removed and the residu was dissolved in 200 ml of EtOAc and 50 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The water-layer was washed with 50 ml of EtOAc once. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was purified by preparative TLC using n-heptane / $MeOCH_2CH_2OMe$: 2 / 3 as the eluent. Yield: 0.10 g of intermediate 22 (20%).

Example A9

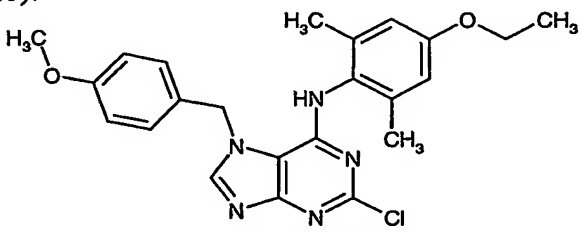
a) Preparation of intermediate 23



Intermediate 16 (prepared according to A7) (50 mg) and intermediate 7 (prepared according to A3b) (5 eq., 144 mg) were dissolved in EtOH and water (3:1, 4 ml). The reaction mixture was stirred at 80°C and checked by TLC and LC/MS. The organic solvents were removed and the residu was dissolved in 100 ml of EtOAc and 50 ml of water. The layers were separated. The water-layer was washed with 50 ml of EtOAc once. The combined EtOAc-layers were washed with 1 M HCl (2x50 ml), 50 ml of

$NaHCO_3$ (sat.) (aq.), dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was purified by preparative TLC using n-heptane / EtOAc : 1 / 1 as the eluent. Yield: 0.04 g of intermediate 23 (49%).

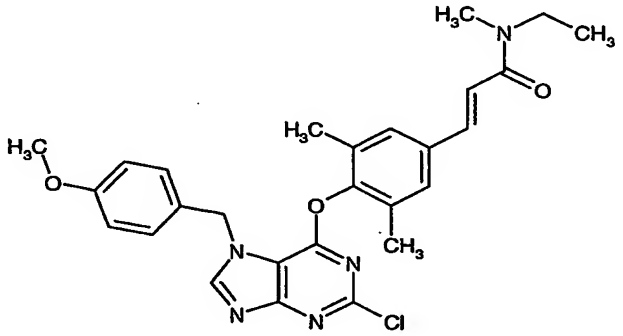
b) Preparation of intermediate 24

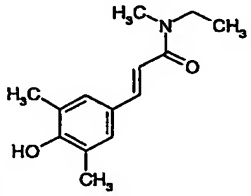


Intermediate 17 (prepared according to A7) (150 mg) and 4-ethoxy-2,6-dimethylbenzenamine (5 eq., 241 mg) were dissolved in EtOH and water (3:1, 8 ml). The reaction mixture was stirred at 80°C and checked by TLC and LC/MS. The organic solvents were removed and the residu was dissolved in 150 ml of EtOAc and 50 ml of water. The layers were separated. The water-layer was washed with 50 ml EtOAc once. The combined EtOAc-layers were washed with 1 M HCl (2x50 ml), 50 ml of $NaHCO_3$ (sat.) (aq.), dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was purified by preparative TLC using n-heptane / $MeOCH_2CH_2OMe$: 2 / 3 as the eluent. Yield: 0.15 g of intermediate 24 (63%).

Example A10

a) Preparation of intermediate 26

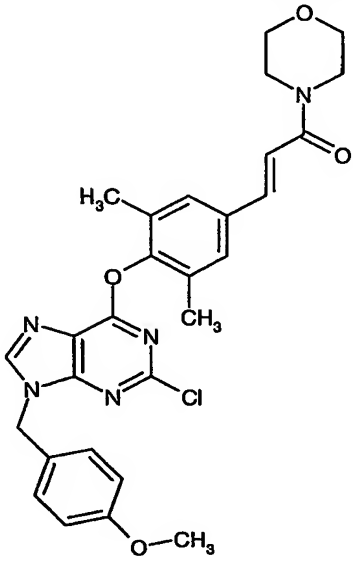


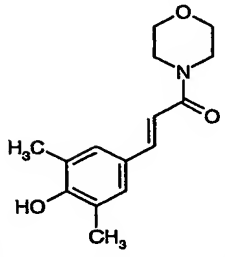


Intermediate 25 (prepared according to A2) (113 mg) was suspended in 10 ml of THF at 20°C and stirred KOtBu (1.0 eq., 60 mg) was added at once. After stirring for 30 minutes at 20°C, a solution of intermediate 17 (prepared according to A7) (1.0 eq., 150 mg) in 10 ml of THF was added dropwise. The reaction mixture was stirred at 20°C and checked by TLC and LC/MS. The organic solvents were removed and the residu was dissolved in 15 ml of DCM and 5 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The DCM-layer was dried (Na_2SO_4), filtered and

concentrated. The residue was purified by preparative TLC using n-heptane / $MeOCH_2CH_2OMe$: 2 / 3 as the eluent. Yield: 0.14 g of intermediate 26 (46%).

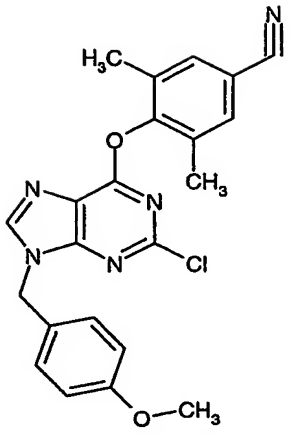
b) Preparation of intermediate 28





Intermediate 27 (prepared according to A2) (84.5 mg) was suspended in 10 ml of THF at 20°C and stirred KOtBu (1.0 eq., 36.3 mg) was added at once. After stirring for 30 minutes at 20°C, a solution of intermediate 16 (prepared according to A7) (1.0 eq., 100 mg) in 10 ml of THF was added dropwise. The reaction mixture was stirred at 20°C and checked by TLC and LC/MS. The reaction-mixture was dissolved in 100 ml of EtOAc and 50 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The water-layer was washed with 50 ml of EtOAc once. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was triturated with diisopropyl ether, filtered and air-dried. Yield: 0.17 g of intermediatte 28 (96%).

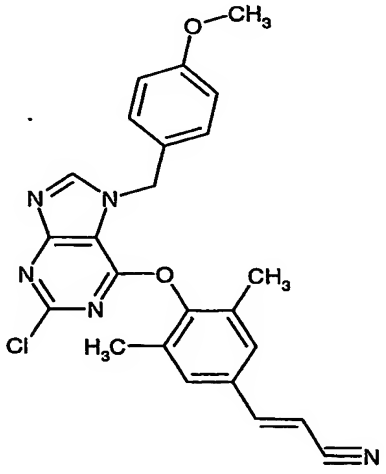
c) Preparation of intermediate 29

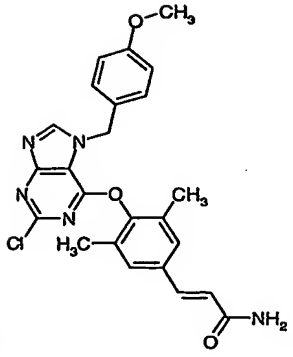


4-Hydroxy-3,5-dimethylbenzonitrile (143 mg) and intermediate 16 (prepared according to A7) (1.0 eq., 300 mg) were mixed with K_2CO_3 (3.0 eq, 402 mg) in 10 ml of 2-BuOH. The reaction mixture was stirred at 100°C and checked by TLC and LC/MS. The organic solvents were removed and the residu was dissolved in 100 ml of EtOAc and 50 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The water-layer was washed with 50 ml of EtOAc once. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was purified by trituration with 10 ml of ethanol. Yield: 0.26 g of intermediate 29 (64%).

Example A11

Preparation of intermediate 31



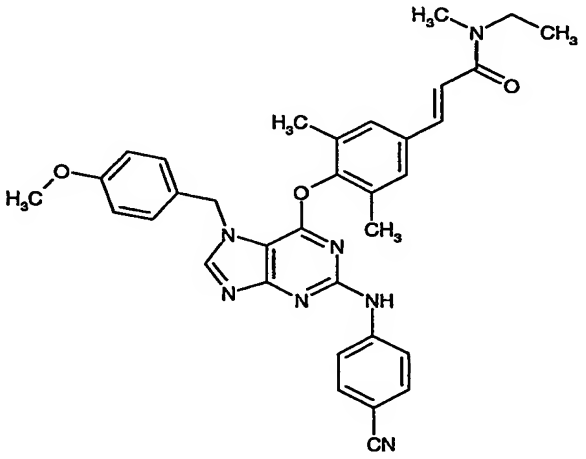


Intermediate 30 (100 mg)(prepared according to A10a) was dissolved in 3 ml $POCl_3$ at 20°C. The reaction mixture was stirred at 20°C and checked by TLC. The reaction mixture was added dropwise to 200 ml of diisopropyl ether. The precipitate was filtered off and was dissolved in 200 ml of EtOAc and 200 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The water-layer was washed with 50 ml of EtOAc once. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. Yield: 0.08 g of intermediate 31 (87%).

B. Preparation of the final compounds

Example B1

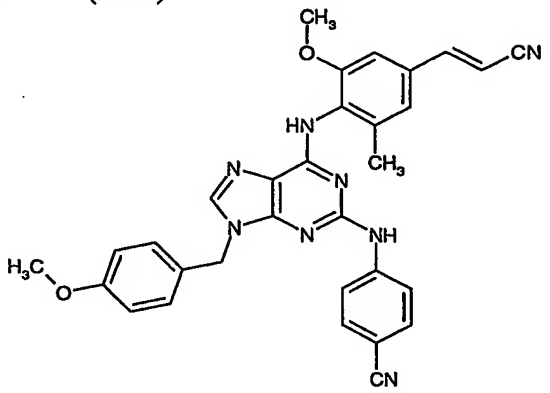
a) Preparation of final compound 1



Intermediate 26 (prepared according to A10a) (117 mg), 4-cyanoaniline (1.5 eq., 48 mg), $Pd(OAc)_2$ (0.06 eq., 6.1mg) and BINAP (0.12 eq., 34 mg) were mixed with Cs_2CO_3 (1.2 eq, 107 mg) in 20 ml of toluene and N_2 was bubbled through the suspension for at least 20 minutes. The reaction mixture was stirred vigorously at 80°C in a sealed reaction-vessel and checked by TLC and LC/MS. The reaction mixture was dissolved in 150 ml of EtOAc and 50 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The water-layer was washed with 50 ml of EtOAc once. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The

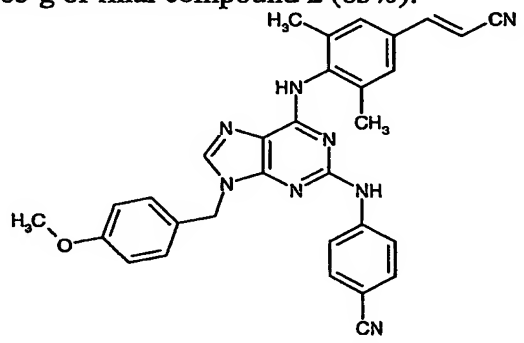
residue was purified by preparative TLC using n-heptane / $MeOCH_2CH_2OMe$: 2 / 3 as the eluent. Yield : 0.11 g of final compound 1 (82%).

b) Preparation of final compound 2



Intermediate 18 (prepared according to A8a) (2.69 g), 4-cyanoaniline (1.5 eq., 1.03 g), $Pd(OAc)_2$ (0.05 eq., 66 mg) and BINAP (0.10 eq., 363 mg) were mixed with Cs_2CO_3 (1.2 eq, 2.47 g) in 75 ml of toluene and argon was bubbled through the suspension for at least 20 minutes. The reaction mixture was stirred vigorously at 80°C in a sealed reaction-vessel and checked by TLC and LC/MS. The reaction mixture was filtered off. The residu was washed once with 25 ml of toluene and dissolved in 300 ml of EtOAc and 100 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The EtOAc-layer was dried (Na_2SO_4), filtered and concentrated. The residu was dissolved in 50 ml of DCM/MeOH 25:1, followed by addition of 500 ml of diisopropylether. The precipitate was filtered off and air-dried. Yield : 2.05 g of final compound 2 (65%).

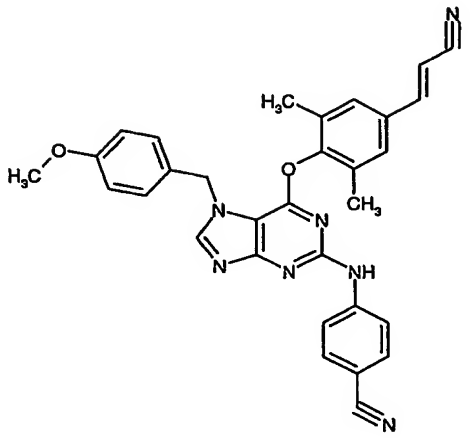
c) Preparation of final compound 3



Intermediate 20 (prepared according to A8b) (242 mg), 4-cyanoaniline (1.5 eq.; 96 mg), $Pd_2(dba)_3$ (0.03 eq.; 15 mg) and BINAP (0.06 eq.; 20 mg) were mixed with Cs_2CO_3 (1.2 eq; 212 mg) in 20 ml of toluene and N_2 was bubbled through the suspension for at least 20 minutes. The reaction mixture was stirred at 80°C in a sealed reaction-vessel and checked by TLC and LC/MS. The reaction mixture was dissolved in 150 ml of EtOAc and 50 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The water-layer was washed with 50 ml of EtOAc once. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was purified by preparative

TLC using n-heptane / $MeOCH_2CH_2OMe$: 2 / 3 as the eluent.Yield : 0.13 g of final compound 3 (46%).

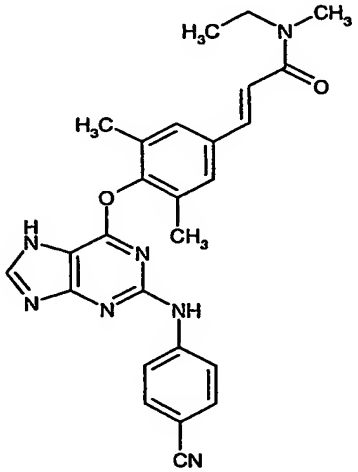
d) Preparation of final compound 4



Intermediate 31 (prepared according to A11) (80 mg), 4-cyanoaniline (1.5 eq.; 32 mg), $Pd_2(dba)_3$ (0.07 eq.; 12 mg) and BINAP (0.14 eq.; 16 mg) were mixed with Cs_2CO_3 (1.2 eq.) in 20 ml of toluene and N_2 was bubbled through the suspension for at least 20 minutes. The reaction mixture was stirred at 80°C in a sealed reaction-vessel and checked by TLC and LC/MS. The reaction mixture was dissolved in 150 ml of EtOAc and 50 ml of $NaHCO_3$ (sat.) (aq.). The layers were separated. The water-layer was washed with 50 ml of EtOAc once. The combined EtOAc-layers were dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was purified by preparative TLC using n-heptane / $MeOCH_2CH_2OMe$: 2 / 3 as the eluent. Yield : 0.08 g of final compound 4 (84%).

Example B2

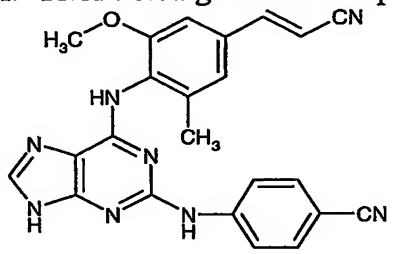
a) Preparation of final compound 5



Final compound 1 (100 mg) was dissolved in 2 ml of TFA. The reaction mixture was stirred at 40 ^{0}C and checked by TLC and LC/MS. The reaction mixture was dilluted with 150 ml of DCM and added dropwise to a concentrated aqueous solution of K_2CO_3

(200 ml), checking pH continuously. Extra DCM (100 ml) was added to dissolve all material. The layers were separated. The DCM-layer was dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated till around 5 ml. The precipitated solid was filtered off and washed once with 5 ml of DCM. Yield : 0.01 g of final compound 5 (15%).

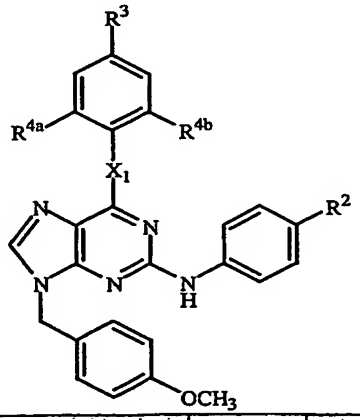
b) Preparation of final compound 6



Final compound 2 (1.79 g) was dissolved in 8 ml of TFA. The reaction mixture was stirred at 60°C and checked by TLC and LC/MS. The reaction mixture was added dropwise to a 2M aqueous solution of NaOH (400 ml), checking pH continuously. EtOAc (800 ml) was added to dissolve all material. The layers were separated. The EtOAc-layer was dried (NaCl (sat.) and Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography using DCM / MeOH : 95 / 5 as the eluent. The product was isolated by trituation with 500 ml of diisopropylether. The precipitate was filtered off and air-dried. Yield: 0.71 g of final compound 6 (51%).

Tables 1, 2 and 3 list the compounds of formula (I) which were prepared according to one of the above examples.

Table 1:



(I)

Co. no.	Exp. no.	R^2	R^3	R^{4a}	R^{4b}	X_1	Physico-chem data.
7	B1c	CN	CH_3	CH_3	CH_3	O	
8	B1b	CN	CH_3	CH_3	CH_3	NH	
9	B1c	CN	$C(CH_3)_3$	CH_3	CH_3	NH	

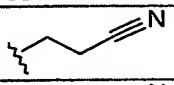
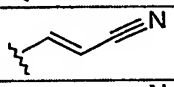
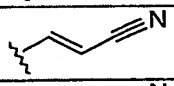
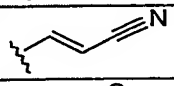
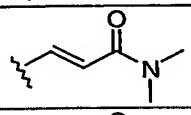
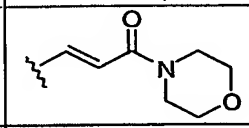
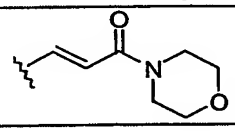
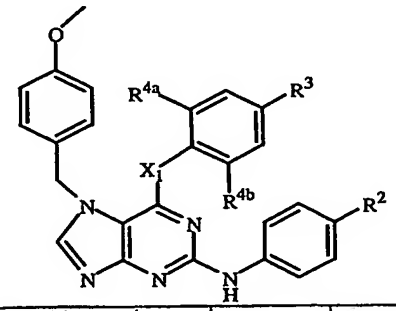
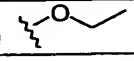
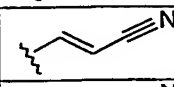
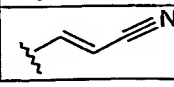
Co. no.	Exp. no.	R^2	R^3	R^{4a}	R^{4b}	X_1	Physico-chem data.
10	B1c	CN	OCH_3	OCH_3	OCH_3	NH	
11	B1c	CN	CN	CH_3	CH_3	O	
12	B1c	CN	CN	CH_3	CH_3	NH	
13	B1c	CN		CH_3	CH_3	NH	
3	B1c	CN		CH_3	CH_3	NH	
14	B1b	CN		Cl	CH_3	NH	
2	B1b	CN		OCH_3	CH_3	NH	
15	B1b	CN		CH_3	CH_3	NH	
16	B1c	CN		CH_3	CH_3	O	
17	B1c	CN		CH_3	CH_3	NH	

Table 2 :



(I)

Co. no.	Exp. no.	R^2	R^3	R^{4a}	R^{4b}	X_1	Physico chem data.
18	B1a	CN		CH_3	CH_3	NH	
4	B1d	CN		CH_3	CH_3	O	
19	B1d	CN		OCH_3	OCH_3	O	

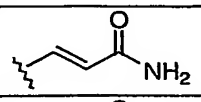
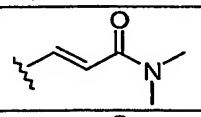
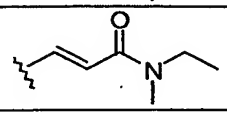
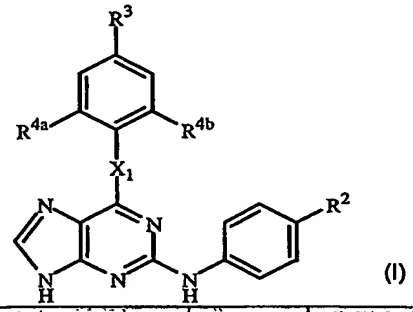
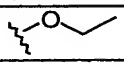
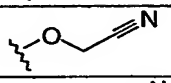
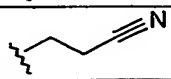
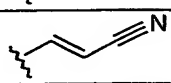
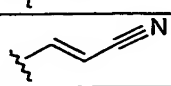
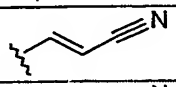
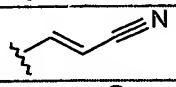
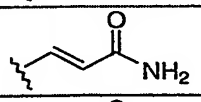
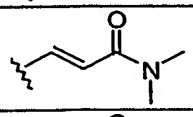
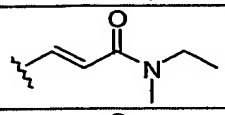
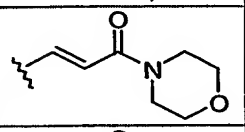
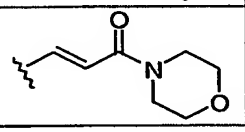
Co. no.	Exp. no.	R^2	R^3	R^{4a}	R^{4b}	X_1	Physico chem data.
20	B1d	CN		CH_3	CH_3	O	
21	B1d	CN		CH_3	CH_3	O	
1	B1a	CN		CH_3	CH_3	O	

Table 3:



(I)

Co. no.	Exp. no.	R^2	R^3	R^{4a}	R^{4b}	X_1	Physico chem data
22	B2b	CH_3	CH_3	CH_3	CH_3	NH	
23	B2b	CN	CH_3	CH_3	CH_3	O	
24	B2b	CN	CH_3	CH_3	CH_3	NH	
25	B2b	CN	OCH_3	CH_3	CH_3	NH	
26	B2b	CN	OCH_3	OCH_3	OCH_3	NH	
27	B2b	CN	$C(CH_3)_3$	CH_3	CH_3	NH	
28	B2b	CN	CN	CH_3	CH_3	O	
29	B2b	CN	CN	CH_3	CH_3	NH	
30	B2a	CN		CH_3	CH_3	NH	
31	B2b	CN		CH_3	CH_3	NH	
32	B2b	CN		CH_3	CH_3	NH	
33	B2a	CN		CH_3	CH_3	O	
34	B2b	CN		CH_3	CH_3	NH	

Co. no.	Exp. no.	R^2	R^3	R^{4a}	R^{4b}	X_1	Physico chem data
6	B2b	CN		OCH_3	CH_3	NH	
35	B2a	CN		OCH_3	OCH_3	O	
36	B2a	CN		CH_3	CH_3	O	
37	B2b	CN		CH_3	CH_3	NH	
5	B2a	CN		CH_3	CH_3	O	
38	B2b	CN		CH_3	CH_3	NH	
39	B2b	CN		CH_3	CH_3	O	

C. Pharmacological example

The pharmacological activity of the present compounds was examined using the following test.

A rapid, sensitive and automated assay procedure was used for the *in vitro* evaluation of anti-HIV agents. An HIV-1 transformed T4-cell line, MT-4, which was previously shown (Koyanagi et al., *Int. J. Cancer*, 36, 445-451, 1985) to be highly susceptible to and permissive for HIV infection, served as the target cell line. In these cells, engineered with GFP (and an HIV-specific promotor), ongoing HIV-infection was measured fluorometrically. Cytotoxicity is measured in the same cells, but engineered with GFP under a constitutional promotor. The infection (or inhibition thereof) of HIV infected cells and the fluorescence of mock-infected cells is assessed by the fluorescent GFP signal generated by the two above mentioned cell lines.

The 50% effective concentration (EC_{50} in μM) was defined as the concentration of compound that reduced the fluorescence of HIV-infected cells by 50%. The 50% cytotoxic concentration (CC_{50} in μM) was defined as the concentration of compound that reduced fluorescence of the mock-infected cells by 50%.

The ratio of CC_{50} to EC_{50} was defined as the selectivity index (SI). The compounds of formula (I) were shown to inhibit HIV-1 effectively. Particular EC_{50}, CC_{50} and SI values are listed in Table 4 hereinbelow.

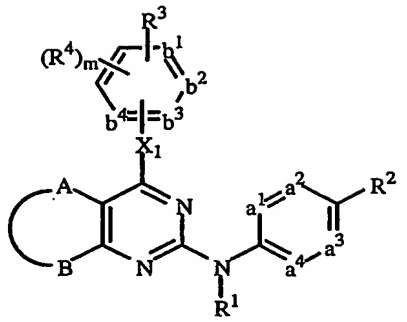
Table 4 lists the pIC_{50} ($-\log IC_{50}$), pCC_{50} ($-\log CC_{50}$) and pSI ($pCC_{50}-pIC_{50}$) values for the compounds of formula (I). For example, a compound with a IC_{50} value of 10^{-9}M, i.e. $pIC_{50} = 9$, and a CC_{50} value of 10^{-5} M, i.e. $pCC_{50} = 5$, has a SI of 10^{-5} M/10^{-9}M = 10.000, i.e. a pSI of 5-9 = -4.

Table 4

Co. No.	pIC_{50}	pCC_{50}	pSI
25	8.5	<4.5	<-4
23	8.2	<4.6	<-3.6
28	9.0	<4.6	<-4.4
21	8.4	4.8	-3.6
20	8.4	5.2	-3.2
13	8.2	5.2	-3.1
26	9.3	5.0	-4.3
19	9.2	<4.6	<-4.6
3	8.5	5.9	-2.6
24	8.4	4.3	-4.1
4	8.4	5.0	-3.4
33	8.5	5.0	-3.5
32	8.3	4.8	-3.5
1	8.4	<4.6	<-3.8
34	8.5	4.8	-3.7
35	8.4	4.9	-3.5
29	8.7	4.9	-3.8
37	8.1	5.4	-2.7
30	8.8	4.8	-4.0
5	8.5	5.3	-3.2
31	9.3	<4.6	<-4.7
14	8.3	5.5	-2.8
6	9.0	6.1	-2.9
2	9.0	5.3	-3.7

Claims

1. A compound of formula



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

$-a^1=a^2-C(R^2)=a^3-a^4=$ represents a bivalent radical of formula

$-CH=CH-C(R^2)=CH-CH=$ (a-1);

$-N=CH-C(R^2)=CH-CH=$ (a-2);

$-CH=N-C(R^2)=CH-CH=$ (a-3);

$-N=CH-C(R^2)=N-CH=$ (a-4);

$-N=CH-C(R^2)=CH-N=$ (a-5);

$-CH=N-C(R^2)=N-CH=$ (a-6); or

$-N=N-C(R^2)=CH-CH=$ (a-7);

$-b^1=b^2-b^3=b^4-$ represents a bivalent radical of formula

$-CH=CH-CH=CH-$ (b-1);

$-N=CH-CH=CH-$ (b-2);

$-N=CH-N=CH-$ (b-3);

$-N=CH-CH=N-$ (b-4); or

$-N=N-CH=CH-$ (b-5);

-A-B- represents a bivalent radical of formula

$-N=CH-NR^{17}-$ (c-1); or

$-NR^{17}-CH=N-$ (c-2);

m is 1, 2, 3 and in case $-b^1=b^2-b^3=b^4-$ is (b-1), then m may also be 4;

R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^2 is cyano; aminocarbonyl; mono- or di(C_{1-4}alkyl)aminocarbonyl; C_{1-6}alkyl; C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl; C_{2-6}alkenyl; C_{2-6}alkenyl substituted with cyano, aminocarbonyl or mono- or

di(C_{1-4}alkyl)aminocarbonyl; C_{2-6}alkynyl; or C_{2-6}alkynyl substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl;

X_1 is $-NR^5$-, -NH-NH-, -N=N-, -O-, -C(=O)-, C_{1-4}alkanediyl, -CHOH-, -S-, -S(=O)$_p$-, -X_2-C_{1-4}alkanediyl- or $-C_{1-4}$alkanediyl-X_2-;

X_2 is $-NR^5$-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)$_p$-;

R^3 is NHR^{13}; $NR^{13}R^{14}$; -C(=O)-NHR^{13}; -C(=O)-$NR^{13}R^{14}$; -C(=O)-R^{15}; -CH=N-NH-C(=O)-R^{16}; cyano; halo; C_{1-6}alkyl; polyhaloC_{1-6}alkyl; C_{1-6}alkyl substituted with one or more substituents each independently selected from cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; C_{1-6}alkyl substituted with hydroxy and a second substituent selected from cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; C_{1-6}alkyloxyC_{1-6}alkyl optionally substituted with one or more substituents each independently selected from cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; C_{1-6}alkyloxy optionally substituted with one or more substituents each independently selected from cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; C_{2-6}alkenyl optionally substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; C_{2-6}alkynyl optionally substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10}, -C(=O)-NR^9R^{10}, -C(=O)-C_{1-6}alkyl or R^7; -C(=N-O-R^8)-C_{1-4}alkyl; R^7 or $-X_3$-R^7;

X_3 is $-NR^5$-, -NH-NH-, -N=N-, -O-, -C(=O)-, -S-, -S(=O)$_p$-, -X_{2b}-C_{1-4}alkanediyl-, -C_{1-4}alkanediyl-X_{2a}-, $-C_{1-4}$alkanediyl-X_{2b}-C_{1-4}alkanediyl, -C(=N-OR^8)-C_{1-4}alkanediyl-;

with X_{2a} being -NH-NH-, -N=N-, -O-, -C(=O)-, -S-, -S(=O)$_p$-; and

with X_{2b} being -NH-NH-, -N=N-, -C(=O)-, -S-, -S(=O)$_p$-;

each R^4 independently is halo, hydroxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyl, formyl, amino, mono- or di(C_{1-4}alkyl)amino or R^7;

R^5 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl or C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^6 is C_{1-4}alkyl, amino, mono- or di(C_{1-4}alkyl)amino or polyhaloC_{1-4}alkyl;

R^7 is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems

may optionally be substituted where possible with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, formyl, C_{1-6}alkylcarbonyl,

C_{3-7}cycloalkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthio, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, -CH(=N-O-R^8), R^{7a}, -X_3-R^{7a} or R^{7a}-C_{1-4}alkyl;

R^{7a} is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems may optionally be substituted where possible with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, formyl, C_{1-6}alkylcarbonyl,

C_{3-7}cycloalkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthio, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, -CH(=N-O-R^8);

R^8 is hydrogen, C_{1-4}alkyl, aryl or arylC_{1-4}alkyl;

R^9 and R^{10} each independently are hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; amino; mono- or di(C_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyl)aminocarbonyl; -CH(=NR^{11}) or R^7, wherein each of the aforementioned C_{1-6}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-4}alkyl)amino, polyhaloC1-4alkyl, polyhaloC1-4alkyloxy, polyhaloC1-4alkylthio, -S(=O)$_p$$R^6$, -NH-S(=O)$_p$$R^6$, -C(=O)$R^6$, -NHC(=O)H, -C(=O)$NHNH_2$, -NHC(=O)$R^6$, -C(=NH)$R^6$, R^7; or

R^9 and R^{10} may be taken together to form a bivalent or trivalent radical of formula

-CH_2-CH_2-CH_2-CH_2- (d-1);

-CH_2-CH_2-CH_2-CH_2-CH_2- (d-2);

-CH_2-CH_2-O-CH_2-CH_2- (d-3);

-CH_2-CH_2-S-CH_2-CH_2- (d-4);

-CH_2-CH_2-NR^{12}-CH_2-CH_2- (d-5);

-CH_2-CH=CH-CH_2- (d-6); or

=CH-CH=CH-CH=CH- (d-7);

R^{11} is cyano; C_{1-4}alkyl optionally substituted with C_{1-4}alkyloxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino or aminocarbonyl; C_{1-4}alkylcarbonyl; C_{1-4}alkyloxycarbonyl; aminocarbonyl; mono- or di(C_{1-4}alkyl)aminocarbonyl;

R^{12} is hydrogen or C_{1-4}alkyl;

R^{13} and R^{14} each independently are C_{1-6}alkyl optionally substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl;

C_{2-6}alkenyl optionally substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl;

C_{2-6}alkynyl optionally substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl;

R^{15} is C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl;

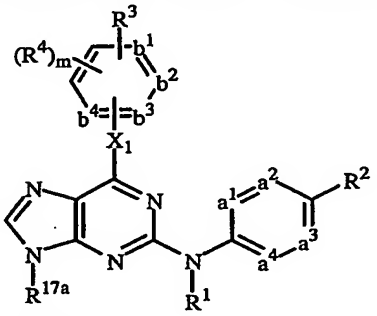
R^{16} is C_{1-6}alkyl optionally substituted with cyano, aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl; or R^7;

R^{17} is hydrogen;C_{1-6}alkyl; or C_{1-6}alkyl substituted with aryl;

p is 1 or 2;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthio, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, R^7 or $-X_3-R^7$.

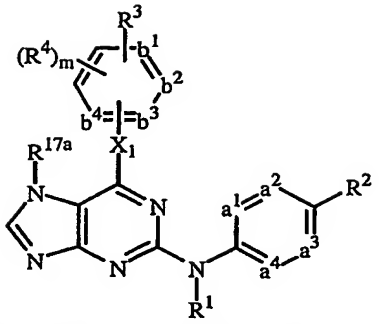
2. A compound according to claim 1 having the formula



(I-a)

wherein $-a^1=a^2-C(R^2)=a^3-a^4=$; $-b^1=b^2-b^3=b^4-$; m; X_1; R^1; R^2; R^3; R^4 are as defined in claim 1 and R^{17a} is C_{1-6}alkyl or C_{1-6}alkyl substituted with aryl.

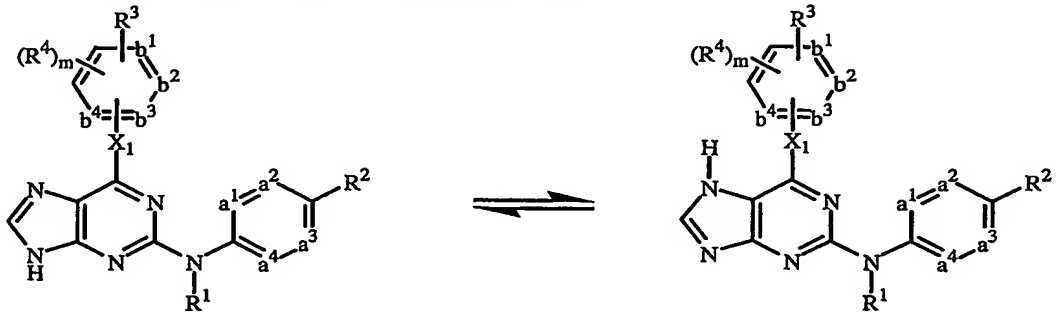
3. A compound according to claim 1 having the formula



(I-b)

wherein $-a^1=a^2-C(R^2)=a^3-a^4=$; $-b^1=b^2-b^3=b^4-$; m; X_1; R^1; R^2; R^3; R^4 are as defined in claim 1 and R^{17a} is C_{1-6}alkyl or C_{1-6}alkyl substituted with aryl.

4. A compound according to claim 1 having the formula



(I-c) (I-d)

wherein $-a^1=a^2-C(R^2)=a^3-a^4=$; $-b^1=b^2-b^3=b^4-$; m; X_1; R^1; R^2; R^3; R^4 are as defined in claim 1.

5. A compound according to any one of claims 1 to 4 for use as a medicine.

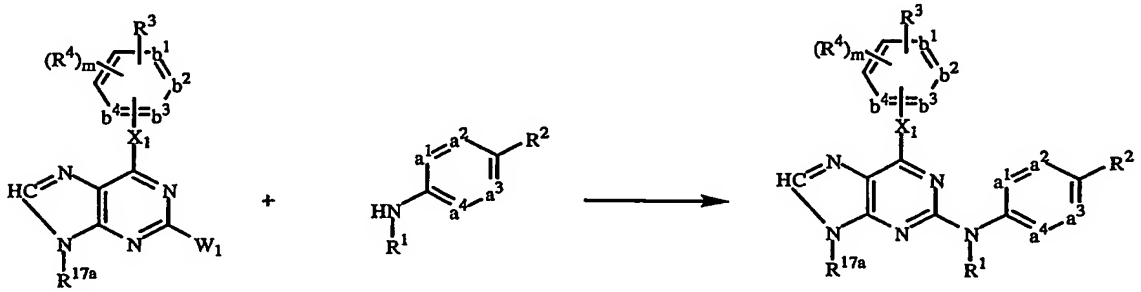
6. The use of a compound as defined in any one of claims 1 to 4 for the manufature of a medicament for the prevention or the treatment of HIV (Human Immunodeficiency Virus) infection.

7. The use of a compound according to claim 6 for the manufacture of a medicament for the prevention or the treatment of drug resistant HIV infection.

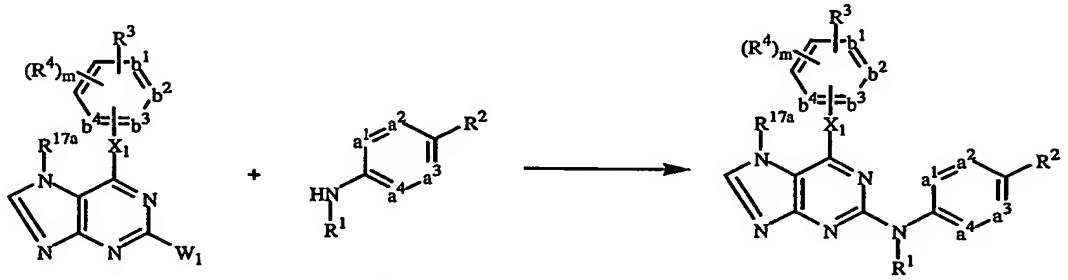
8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 4.

9. A process for preparing a pharmaceutical composition according to claim 8 characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 4 is intimately mixed with a pharmaceutically acceptable carrier.

10. A process for preparing a compound as claimed in claim 1, characterized by a) reacting an intermediate of formula (II-a) or (II-b) wherein W_1 represents a suitable leaving group, with an intermediate of formula (III) in the presence of a suitable catalyst, a suitable ligand, a suitable base, and a suitable solvent,



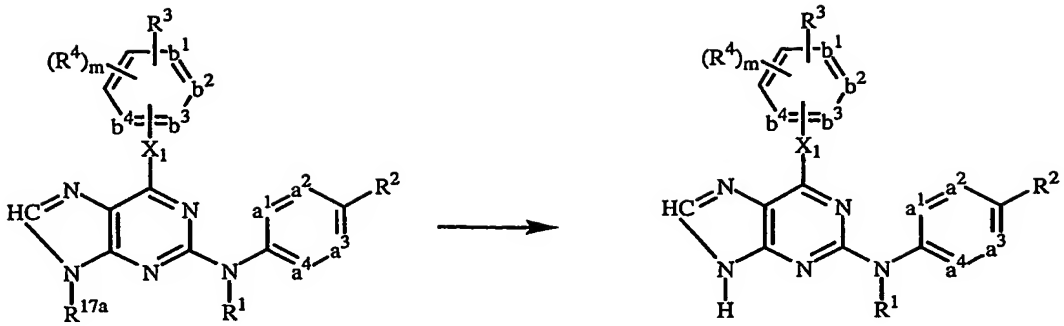
(II-a) (III) (I-a)



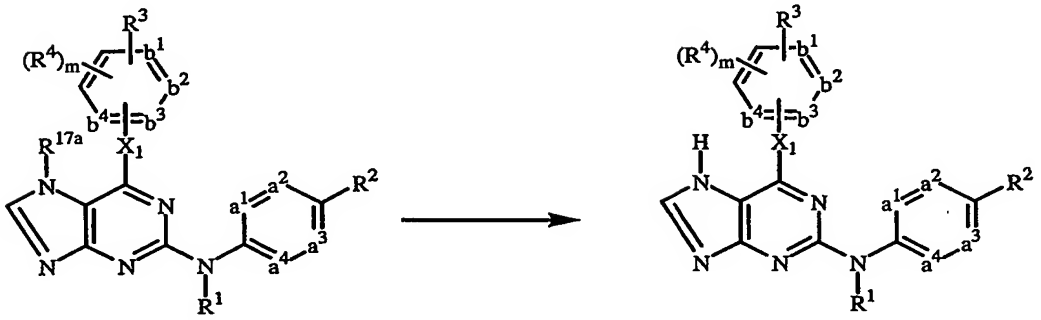
(II-b) (III) (I-b)

wherein $-a^1=a^2-C(R^2)=a^3-a^4=$; $-b^1=b^2-b^3=b^4-$; m; X_1; R^1; R^2; R^3; R^4 are as defined in claim 1 and R^{17a} is C_{1-6}alkyl or C_{1-6}alkyl substituted with aryl;

b) converting a compound of formula (I-a) or (I-b) wherein R^{17a} is C_{1-6}alkyl or C_{1-6}alkyl substituted with aryl into a compound of formula (I-c) or (I-d) with a suitable acid,



(I-a) (I-c)



(I-b) (I-d)

wherein $-a^1=a^2-C(R^2)=a^3-a^4=$; $-b^1=b^2-b^3=b^4-$; m; X_1; R^1; R^2; R^3; R^4 are as defined in claim 1;

or, if desired, further converting compounds of formula (I) into each other following art-known transformations; or further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or conversely, converting the acid addition salt form into the free base by treatment with alkali; or, if desired, preparing stereochemically isomeric forms, *N*-oxide forms or quaternary amines thereof.

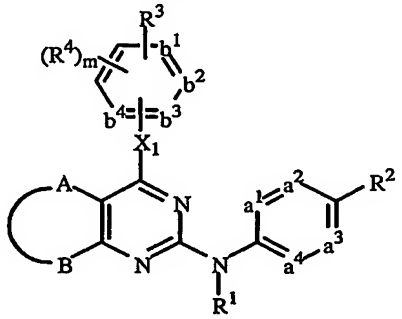
11. A product containing (a) a compound according to any one of claims 1 to 4, and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in the treatment of HIV infection.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) a compound according to any one of claims 1 to 4, and (b) another antiretroviral compound.

ABSTRACT

HIV REPLICATION INHIBITING PURINE DERIVATIVES

This invention concerns a HIV replication inhibiting purine derivative of formula



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein -a^1=a^2-C(R^2)=a^3-a^4= represents -CH=CH-C(R^2)=CH-CH= (a-1); -N=CH-C(R^2)=CH-CH= (a-2); -CH=N-C(R^2)=CH-CH= (a-3); -N=CH-C(R^2)=N-CH= (a-4); -N=CH-C(R^2)=CH-N= (a-5); -CH=N-C(R^2)=N-CH= (a-6); -N=N-C(R^2)=CH-CH= (a-7); -b^1=b^2-b^3=b^4- represents -CH=CH-CH=CH- (b-1); -N=CH-CH=CH- (b-2); -N=CH-N=CH- (b-3); -N=CH-CH=N- (b-4); -N=N-CH=CH- (b-5); -A-B- represents -N=CH-NR^{17}- (c-1) or -NR^{17}-CH=N- (c-2); m is 1, 2, 3 or 4; R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; substituted C_{1-6}alkyl; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl; R^2 is cyano; aminocarbonyl; mono- or di(C_{1-4}alkyl)aminocarbonyl; C_{1-6}alkyl; substituted C_{1-6}alkyl; C_{2-6}alkenyl; substituted C_{2-6}alkenyl; C_{2-6}alkynyl; or substituted C_{2-6}alkynyl; X_1 is–NR^5-, -NH-NH-, -N=N-, -O-, -C(=O)-, C_{1-4}alkanediyl, -CHOH-, -S-, -S(=O)$_p$-, -X_2-C_{1-4}alkanediyl- or –C_{1-4}alkanediyl-X_2-; R^3 is NHR^{13}; $NR^{13}R^{14}$; -C(=O)-NHR^{13}; -C(=O)-$NR^{13}R^{14}$; -C(=O)-R^{15}; -CH=N-NH-C(=O)-R^{16}; cyano; halo; C_{1-6}alkyl; polyhaloC_{1-6}alkyl; substituted C_{1-6}alkyl; C_{1-6}alkyl substituted with hydroxy and a second substituent; optionally substituted C_{1-6}alkyloxyC_{1-6}alkyl; optionally substituted C_{1-6}alkyloxy; substituted C_{2-6}alkenyl; substituted C_{2-6}alkynyl; -C(=N-O-R^8)-C_{1-4}alkyl; R^7 or –X_3-R^7; R^4 is halo, hydroxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyl, formyl, amino, mono- or di(C_{1-4}alkyl)amino or R^7; their use as a medicine, their processes for preparation and pharmaceutical compositions comprising them.